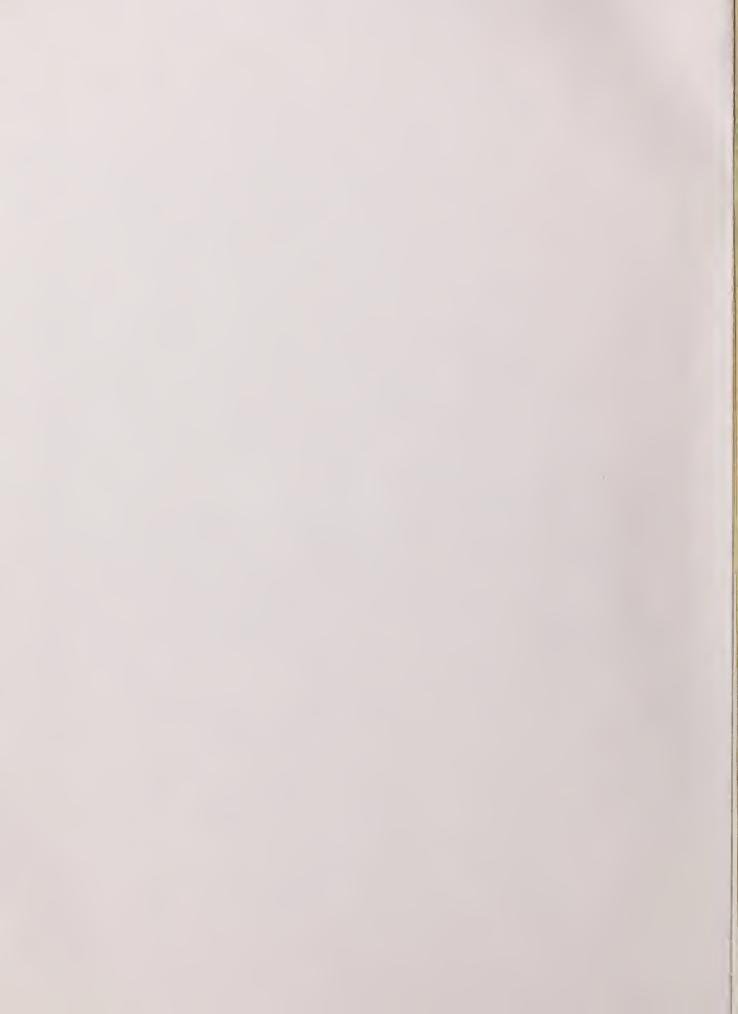


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Columna del Editor



En las páginas que siguen puede encontrar el lector artículos originales sobre temas diversos producto de la experiencia clínica de médicos puertorriqueños. Puede notarse que uno de estos estudios clínicos proviene de un prominente centro de investigación de los E.E.U.U. Es cada día más frecuente casos como este donde nuestros médicos aún trabajando fuera del país envían sus trabajos al Boletín de la Asociación Médica de Puerto Rico. En el caso del artículo del Dr. Vivas creemos que la información que provee es de gran importancia. Sin duda será de beneficio para esclarecer las ya suficientemente confusas manifestaciones clínicas del lupus eritematoso sistémico y las espondiloartritis seronegativas. Los otros dos estudios clínicos que le siguen tienen un contenido de gran interés científico y reflejan la "experiencia local", que es una de las principales razones de ser de nuestra revista. Las secciones fijas mensuales de autoevaluación, nutrición y noticias completan este número que la Junta Editora ha preparado para sus lectores.

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Rafael Villaviciencio, MD, FACC Presidente Junta Editora Boletín Asociación Médica de Puerto Rico

BOLETIN



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NUESTRA PORTADA

La Armada Invencible - Acrílico del Dr. José R. Oliver

El autor nació en Arecibo, el 29 de mayo de 1901. En 1910 recibió clases de pintura de María Cadilla de Martínez y al año siguiente lo llevan a España, donde sus profesores de arte fueron el Padre J. Calasanz, el Padre Molins y Casto Oliver, en Barcelona. Vivió en Madrid y París, donde pintó e hizo esculturas y esmaltes al fuego.

En 1928 entró a formar parte del grupo de expositores de Galerías Layetanas, y al estallar la guerra en España regresa a Puerto Rico. Pinta varios murales, gana premios en el Ateneo y el Instituto de Cultura, y da clases en la Universidad de Puerto Rico. Cuando se funda la Escuela de Artes Plásticas es designado su director donde realizó una gran labor en favor de la enseñanza del arte en Puerto Rico.

Ha tenido varias exposiciones en Barcelona, México, Trinidad, Nueva York, París y Madrid. Hizo el mural en mosaico sobre la conquista y colonización de la Isla, en la rotonda del Capitolio de San Juan.

La obra que aparece en nuestra portada pertenece a la colección privada del licenciado J. Trías Monje. La Junta Editora agradece a la Galería Rechany en Hato Rey su ayuda para lograr publicar esta obra en nuestra portada.

REVIEW ARTICLES

Chest Pain of Esophageal Origin

Wilmer Rodríguez, M.D.

Between 10-30% of patients referred to cardiology clinics or admitted to coronary care units appear to be free of atherosclerotic heart disease. Furthermore up to 20% of coronary angiograms are either normal or show trivial lesions considered unlikely to account for patients symptoms. In this group very few patients will have a characteristic history and electrocardiographic changes to suggest coronary spasm, a small percentage may a have underlying pulmonary, musculoskeletal or arthritic conditions. Most of the remaining will have an underlying esophageal disorder as a cause of pain; they will be the subject of this discussion.

Esophageal Causes of Chest Pain

The esophageal causes of chest pain are classified in table 1 based on their etiology. Organic disorders such as esophagitis, tumors, ulcerations, stricture and infection should be considered in every patient and excluded by xrays or endoscopic study of the esophagus. Motor disorders of the esophagus (EMD'S) are being recognized

TABLE I

Esophageal Causes of Chest Pain

Organic

Esophagitis- Strictures, Ulcers Esophageal Cancer Infections- Herpes, Candida Caustic Injury Radiation

Primary Motility Disorders

Achalasia
Diffuse Esophageal Spasm
Vigorous Achalasia
"Nutcracker" Esophagus
Acid Induced Motor Disturbances
Non-Specific Motor Disturbances

Secondary Motility Disorders

Scleroderma
Diabetes
Chronic Idiopathic Intestinal Pseudo-Obstruction

Staff Gastroenterologist, San Pablo Hospital, Bayamón, Puerto Rico Request for reprints: Torre de San Pablo 905, Bayamón, Puerto Rico, 00619 more frequently as a cause of chest pain. When underlying organic esophageal disorders are excluded, we label this condition as primary. There are other conditions in which the esophageal abnormalities are only a secondary feature of more generalized disease (scleroderma, diabetes, ect.). The greater availability of esophageal manometry allows these entities to be more frequently recognized and specific criteria are described for their diagnosis.

Crucial to the definition of abnormal esophageal motility is a careful documentation of normal values in a standarized manner. With the advent of pneumohydraulic infusions systems of low compliance, normal manometric values have been defined individually in many laboratories. The most accepted values are listed on table 2.

TABLE II

Normal Esophageal Manometric Values

Lower Esophageal Sphincter (LES)

- -Mean LES pressure = 10-26 mmHg
- -Mean Relaxation Pressure 90% Baseline after 6 wet swallows

Esophageal body

- -Mean peristalic amplitude in distal esophagus = 50-110 mmHg
- -Mean duration of peristaltic wave in distal esophagus 1.9-5.0 sec.
- -Absence of spontaneous, repetitive or simultaneous contractions
- -Single wave forms (no more than two peaks)

Manometric Abnormalities in Primary EMD'S

Achalasia: There are two main functional defects in this condition, obstruction at the gastroesphageal junction and abnormal esophageal peristalsis. A probable diagnosis is made by barium swallow on the presence of a dilated esophagus with tapered narrowing of the lower end. Manometry is diagnostic as evidenced by elevated lower esophageal sphincter pressure with incomplete or no relaxation on swallowing and absence of peristalsis of the esophageal body.

Diffuse Esophageal Spasm: This condition is not as specifically defined or characterized, sometimes resulting in considerable confusion in establishing a diagnosis. The findings of a "corkscrew" appearance on barium swallow is highly suggestive but confirmation depends on the manometric findings of multiple simultaneous and

repetitive esophageal body contractions that occur spontaneously or with a swallow.

Vigorous Achalasia: This designates the combined manometric finding of hypertensive lower esophageal sphincter pressure and repetitive simultaneous contractions as seen in esophageal spasm. There is evidence that diffuse esophageal spasm and achalasia are related, they might represent different clinical manifestations of the same pathologic process. The manometric transition of spasm to achalasia has been documented on various occassions.

"Nutcracker" Esophagus: It is characterized by severe crushing chest pain and manometrically shows very high amplitude contractions.

Acid Induced Esophageal Abnormalities: Infusion of acid into the esophagus may produce abnormal motility in some patients including contractions resembling spasm. On most cases histologic evidence of inflammation in the lower third of the esophagus can be found. Manometry and pH studies are sometimes necessary to establish the degree of reflux and quantitate the pressure of the lower esophageal sphincter.

Non-Specific Disorders: A great number of patients with "abnormal" motility findings that cannot be easily categorized are included in this group. The manometric findings show a variety of non-specific tracings: high lower sphincter pressure, low amplitude contractions, absent peristalsis or intermittently repetitive contractions.

Scleroderma: Manometric evaluation in these patients is useful to asses the stage of progression of the motor disturbance. The findings can range from normal peristalsis and normal sphincter pressure in mild cases to aperistalsis of the distal third of the esophagus and abscence sphincter pressure with free reflux in the advanced cases.

Diabetes: Can produce a peripheral neuropathy in the advanced cases. The manometric findings are those of a reduction in normal esophageal body peristalsis.³⁻⁵

Provocative Tests

Several techniques have been suggested over the years to provide ways of provoking episodes of chest pain in patients with esophageal motility disorders. These include; iced water swallows, intra-esophageal instillation of acid and injections of bethanecol, edrophonium or ergonovine.^{6, 7} At the present time the use of edrophonium chloride (10mg IV) has proven to be the best available provocative agent in the diagnosis of esophageal dysmotility causing chest pain.⁸ A recent study reports that aproximately 20% of patients with noncardiac chest pain will have changes in their manometric tracings with chest pain provoked by edrophonium.⁶

Therapy

Appropriate therapy for the primary esophageal motility disorders other than achalasia is often perplexing to the clinician. A wide variety of therapies have been used including nitrates, sedatives, hydralazine, esophageal dilatation and surgery all with conflicting results and none in controlled clinical trials. Recent studies using

calcium channel blockers have shown a potential use for these drugs but more experience in a randomized fashion is needed.^{10, 11}

Conclusions

With the advent of more sophisticated esophageal manometry systems, it has been widely demonstrated that peristaltic events in the esophagus can be accurately and reproducibly recorded. Esophageal motor abnormalities do cause chest pain. We must continue to attempt to define their importance, and probably offer them a more reasonable therapeutic alternative than rassurance.

El esófago es la causa de una gran parte de Resumen: los síndromes de dolor de pecho donde la enfermedad cardíaca ha sido excluída. A pesar de la frequencia con la que se pueden ver estos pacientes, solo en unos pocos se puede comprobar organicidad esofágica. Con el reciente refinamiento en la técnica de manometría esofágica y la identificación de valores normales, diferentes patrones anormales de motilidad esofágica han sido establecidos. En un intento para aumentar la sensitividad y especificidad de la manometría esofágica, varios compuestos farmacológicos se han usado para provocar estos patrones y síntomas. Hasta ahora la mayoría de las modalidades terapeúticas tratadas en estos pacientes han sido infructuosas, pero el uso de bloqueadores de calcio ofrece mucha promesa. Debemos reconocer la importancia en el diagnóstico y tratamiento de pacientes con estas condiciones.

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Progreso Terapeútico: VANCOMICINA

Rita Cuevas, MS IV Jorge Sánchez, M.D. Héctor F. Gorbea, M.D. Carlos H. Ramírez-Ronda, M.D., F.A.C.P.

Resumen: La vancomicina es un antibiótico bactericida con un espectro de acción en contra de Estafilococo aureus, Estafilococo epidermidis, Estreptococo pyogenes, Estreptococo pneumoniae y Estreptococo viridans. En su forma oral, es la terapia de elección para la colitis causada por Clostridium difficile (colitis asociada a antibióticos). La combinación sinergística de vancomicina y gentaminación se absorbe pobremente del tracto gastrointestinal y debe administrarse en forma endovenosa. La media vida normal es de unas 6 horas, pero en pacientes con fallo renal, una sola dosis de 1 gm. provee efectos terapeúticos por 7-10 días. Normalmente, 80% de ella se excreta por el riñón. Se distribuye ampliamente en los tejidos y cura las meninges cuando están inflamadas. No puede removerse por hemodiálisis o diálisis peritoneal. Su uso clínico mayor ha sido en el tratamiento de infecciones estafilocóccicas serias en pacientes alérgicos a los antibióticos B-lactámicos o en infecciones con estafilococos resistantes a la meticilina. Se usa en el tratamiento de colitis asociada a antibióticos por cepas de C. difficile. Puede usarse en profilaxis de endocarditis infecciosa en pacientes alérgicos a la penicilina que van a ser operados y en los cuales hay riesgo de bacteremia por estreptocococos; también en el tratamiento de infecciones estafilocóccicas de los desvíos (intravasculares) de pacientes en hemodiálisis. Sus efectos secundarios principales son la nefrotoxicidad y ototoxicidad, además de tromboflebitis. Su infusión endovenosa rápida puede producir hipotensión, taquipnea, náusea y vómitos.

L a vancomicina es un antibiótico de acción bactericida en contra de los estafilococos y estreptococos, así como en contra de pneumococos y bacilos grampositivos como el de la difteria y aún el enterococo, en acción sinergística con un aminoglucósido. Es un derivado del *Streptomyces orientalis*, un actinomiceto aislado mayormente de muestras de tierra en Indonesia y la India; fue introducido en 1956 y ya dos años después, su uso era generalizado. Tiene un peso molecular de 1500 y se presenta de forma comercial como el clorhidrato, un polvo blanco soluble en agua hasta una concentración de más de 100 mg/ml.¹, ², ³

Modo de Acción y Farmacología

Es un antibiótico bactericida que actúa inhibiendo la síntesis de la pared de las bacterias; esto lo hace uniéndose a precursores en la formación de esta importante estructura bacteriana, específicamente a la porción precursora D-alanyl-alanina. El desarrollo de resistencia durante su terapia es raro, y cuando lo hace, es de una forma lenta y gradual. Su concentración inhibitoria mínima (MIC) es muy cercana a la bactericida (MBC), lo cual se considera deseable, sobretodo en el tratamiento de organismos tolerantes como es el estafilococo. En presencia del enterococo, esta diferencia escasa entre el MIC y el MBC se hace mucho más amplia; por eso, en el tratamiento del enterococo hay que añadir un aminoglucósido para obtener una acción sinergística.⁴

La vancomicina, usualmente se administra por vía endovenosa u oral; su administración intramuscular es muy dolorosa y no se usa. La infusión intermitente en más de 30-60 minutos se prefiere a la continua y rápida, ya que ésta puede producir reacciones eritematosas o de urticaria alarmantes, sobre todo en el tronco superior ("Red Neck Syndrome"). Puede producir episodios de tromboflebitis, los cuales pueden evitarse administrándola por goteo o infusión intermitente, diluída en 100-250 cc D/W 5% o en volúmenes mayores si el paciente puede tolerarlos. La dosis para adultos suele ser de 500 mg cada 6 horas. La dosis diaria para niños es de 40 mg/kg de peso al día en dosis divididas cada 6 horas. La vancomicina se absorbe pobremente cuando se administra por vía oral y grandes cantidades se eliminan en las heces. Por la vía endovenosa, la administración de 500 mg produce concentraciones séricas de 6-10 ug/ml en 1-2 horas; tiene una media vida de unas 6 horas, 10% de la dosis administrada se une a proteínas plasmáticas; el 80-90% de la misma se excreta por vía renal y penetra bien los tejidos, incluso el líquido cefalorraquídeo cuando hay inflamación de las meninges. Niveles bactericidas ocurren en el líquido pleural, ascítico, pericárdico y sinovial, pero sólo pequeñas cantidades en la bilis.5

El riñón es el órgano primario de eliminación; más del 90% de la dosis administrada es excretada en el término de 24 horas; la media vida en pacientes normales es de 6-8 horas, pero en pacientes anúricos, se prolonga hasta 8-10 días. Los esquemas de su administración en pacientes con fallo renal varían, se prefiere prolongar los intérvalos de administración en lugar de disminuir las dosis individuales porque es un método más simple y hay seguridad en obtener niveles asociados séricos de forma más estable. La vancomicina no se remueve con la hemodiálisis y aunque se difunde bien el líquido ascítico, la depuración

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peritoneal es pobre; aproximadamente 65% de una dosis intraperitoneal se absorbe durante un período de 4 horas de diálisis por esa vía.⁶

Usos Clínicos

La vancomicina tiene 2 tipos de usos: profilácticos y terapeúticos. Profilácticamente, ha sido utilizada para prevenir ciertas infecciones causadas por cocos grampositivos, como en la cirugía cardiaca para implantación de válvulas prostéticas, por su excelente actividad contra E. aureus y E. epidermidis. En combinación con eritromicina, ha sido usada para prevenir endocarditis en aquellos pacientes propensos a adquirir la condición y que son alérgicos a penicilina y van a ser intervenidos en procedimientos orales y del tracto respiratorio superior, combinada con gentamicina en pacientes de cirugía del tracto gastrointestinal. También en la prevención y tratamiento de pacientes en hemodiálisis crónica con infecciones de desvíos.⁷ Entre sus usos terapeúticos, la vancomicina se administra en infecciones serias causadas por estafilococos resistentes a la metilicina, como neumonías, empiemas, endocarditis, osteomielitis y abscesos de tejido blando. Puede usarse empíricamente en pacientes muy propensos a adquirir infecciones con estafilococos resistentes a la metilicina; este grupo de pacientes incluye los que han estado hospitalizados por largo tiempo, los diabéticos, los que tienen insuficiencia vascular periférica, quemaduras, y neoplasias malignas. Se administra el antibiótico empíricamente hasta que estén disponibles los resultados de los cultivos. Por vía oral, es el tratamiento de elección para colitis asociada a antibióticos y producida por C. difficile^{10, 11, 12} Es también la droga de elección en pacientes alérgicos a la penicilina con infecciones severas causadas por estafilococos. La vancomicina puede interactuar con otras drogas dadas concomitantemente, como son cloranfenicol, esteroides adrenales y meticilina, produciendo su inactivación.

Reacciones Adversas y Precauciones

Anafilaxis, diferentes tipos de erupciones en la piel, flebitis y dolor en el sitio de la inyección son reacciones encontradas ocasionalmente; fiebre y escalofríos también pueden ocurrir durante su administración. 13 La ototoxicidad, que puede ser permanente, se produce con dosis plasmáticas altas del medicamento (>30 ug/ml); el efecto empeora si se administran otros aminoglucósidos o diuréticos concomitantemente. La nefrotoxicidad se veía anteriormente con mucha frecuencia, pero su incidencia ha disminuído debido al uso más cuidadoso de la droga y al seguimiento frecuente del paciente con niveles séricos de la droga y de los parámetros renales adecuados. Su uso concomitante con otros agentes potencialmente nefrotóxicos y diuréticos aumenta la nefrotoxicidad, así como también dijimos, la ototoxicidad. Otros efectos adversos que se han reportado son el surgimiento de neutropenia. Se ha visto este efecto en algunos casos de pacientes renales después de haber recibido la última dosis de vancomicina concomitantemente con el surgimiento de una erupción en la piel de hipersensitividad, hasta en un período de 6 semanas después de recibir la

última dosis, lo que sugiere algún tipo de reacción inmunológica envuelta. ¹⁴ La forma de presentación del medicamento es en frascos de 10 gramos para reconstitución de la solución oral (con 115 cc de agua destilada): 6cc de esta solución equivale a 500 mg de vancomicina. Para la administración parenteral, viene en frascos de 10 cc (500 mg). La dosis usual por esta vía es de 500 mg endovenoso cada 6 horas, haciendo los ajustes necesarios en pacientes renales como antes mencionamos. Para su uso oral, la dosis usual es de 125 a 250 mg cada 6 horas por 7 a 10 días.

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What can you do for hypertensives like Manuel G?

Controlled

Current medication brought blood pressure from 172/110 to 148/92 mmHa.

Family man

Loves kids...his wife would like several more.

Successful

Too preoccupied on business trips to remember his pills.

Impotent

Blames his current blood pressure medication.



Rely on one-tablet-a-day dosage and cardioselectivity.

"Real life" efficacy

Manuel G represents 5,314 men age 40 to 55 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

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Only 0.4% of the patients in the evaluation reported sexual performance problems²—making TENORMIN an excellent choice for men like Manuel G, who may have become impotent on other antihypertensive agents.

*Cardioselectivity denotes a relative preference for β₁ receptors, located chiefly in cardiac tissue. This preference is not absolute

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects³ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



For Manuel G...and virtually all your hypertensive patients

TENORMIN® (atended)





and virtually all your hypertensive patients TENORMIN® (atenolol)

DESCRIPTION: TENORMIN* (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide. 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]. Atenolol (tree base) has a molecular weight of 266 lt is a relatively polar hydrophilic compound with a water solubility of 26 5 mg·ml at 37° C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg·ml at 25° C) and less soluble in chloroform (3 mg·ml at 25° C) INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hyportension. It may be used allowed or concomitantly with other antibypergensive agents, nadicularly with a

A beta,-selective blocking agent for hypertension

sion. It may be used alone or concomitantly with other antihypertensive agents, particularly with a

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS) WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential nazard of turther depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenoloi slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac tailure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic. TENORMIN therapy should be withdrawn.

Ison and cluretic. I ENORMIN therapy should be windrawn. Isochemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated it with-

drawal symptoms occur Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, how-ever, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta;-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic

the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene. TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg. dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg. protound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients it a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg. tachycardia) of hyperthyrodism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with

should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with
impaired renal function (see DOSAGE AND ADMINISTRATION)

Drug Interactions: Catecholamine-depleting drugs (eg. reserpine) may have an additive effect
when given with beta-blocking agents Patients treated with TENORMIN plus a catecholamine
depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine
concurrently, the beta blocker should be discontinued several days before the gradual withdrawal
of clonding.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of altenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended duman dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively)

respectively)

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a doserelated increase in embryo, tetal resorptions in rats at doses equal to or greater than 50 mg/kg or
25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12 5 times the
maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since

most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS: Most adverse effects have been midl and transient Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg., by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo—treated patients than when these reactions were volunteered. Where trequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

is similar, causar relationality is uncertain. The following adverse-reaction data present frequency estimates in terms of percentages. It is trom the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects) and the first studies (volunteered side effects) are studies (volunteered side effects).

teered and elicited side effects)

U.S. TUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)
CENTRAL NERYOUS SYSTEM/NEUROMUSCULAR dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), drearming (0%-0%)
GASTROINTESTINAL, diarrhea (2%-0%), nausea (4%-1%)
RESPIRATORY (See WARNINGS) wheeziness (0%-0%), dyspnea (0.6%-1%)
TOTALS ULS AND FOREIGN STUDIES*

TOTALS U.S. AND FOREIGN STUDIES:

TOTALS U.S. AND FOREIGN STUDIES:
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR dizziness (13%-6%), vertigo (2%-0.2%), light-headeness (3%-0.7%), itredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL diarrhea (3%-2%), nausea (3%-1%)
RESPIRATORY (see WARNINGS) wheeziness (3%-3%), dyspnea (6%-4%)
MISCELLANEOUS: There have been reports of skin rashes and /or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. ed following cessation of therapy

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolol)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and

bances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomicocutaneous syndrome associated with the beta blocker practiol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practicol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency freatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart tailure, hypotension, bronchospasm, and hypoglycemia

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested it warranted.

Bradycardia: Atropine or another anticholinergic drug
Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.
Congestive Heart Failure: Conventional therapy
Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis
Bronchospasm: Antinophylline, isoproterenol, or atropine
Hypotension

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to durent therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is

unlikely to produce any further benefit

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diureitos, hydralazine, prazosin, and alpha-methyldopa

Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1 73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment

Creatinine Clearance (ml min 173 m²)	Atenolol Elimination Halt-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked talls in blood pressure can occur. HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 105 embossed on the other side are supplied in monthly calendar packages of 28 lablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round. Ilat, uncoated, white tablets with Stuart embossed on one side and NDC No 101 embossed on the other side are supplied in boffles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat light and most time. Store unit-dose and calendar packages at controlled from the store of the

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room

References: 1. Data on file, Stuart Pharmaceuticals. 2. Herman RL, Lamdin E, Fischefti JL, Ko HK. Postmarketing evaluation of atenolol (Tenormin*). A new cardioselective beta-blocker. *Curr Ther Res* 1983, 33(1).165-171. 3. Zacharias FJ: Comparison of the side effects of different beta blockers in the treatment of hyperension. *Primary Cardiol* 1980, 6 (suppl 1):86-89.



ESTUDIOS CLINICOS

Sacroilitis in Male Systemic Lupus Erythematosus

Jaime Vivas, M.D.*
Nicholas A. Tiliakos, M.D.**

Sacroiliac joints, as a rule, are not involved in connective tissue diseases; and the anticipation of coexistence of systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS) is extremely rare. However lupoid sacroarthropathy, an association of "lupoid" syndromes with seronegative spondyloarthritic features, has been described. This study was undertaken to determine the prevalence of sacroilitis in male patients with SLE and its variants.

Methods

All male patients, who met the 1982 revised criteria for classification of SLE or the clinical and serologic criteria for mixed connective tissue disease (MCTD) and followed in the Rheumatology Clinic of the Veterans Administration Medical Center (VAMC), Atlanta, Georgia during the period 1980-1983 were reviewed. Eighteen patients with these diagnoses had been followed in the Rheumatology Clinic over the period of time encompassed by the study. Sixteen patients available were evaluated radiologically and clinically for the presence of sacroiliitis. None of the patients in this group has had enteropathies, prostatitis, urethritis, colitis, psoriasis, chronic mucositis, iritis, previously diagnosed spondyloarthropathy, or a family history of AS.

Results

From the sixteen patients (age 23-63 years) who were evaluated, thirteen patients had SLE, and three MCTD. Seven of the patients were black (2 MCTD, 5 SLE) and nine were white (2 MCTD, 7 SLE). The duration of the illness varied from 8 months to 15 years. All but four patients were on prednisone (1 to 60mg daily) for a period of 1 to 10 years. Based on the presence of back pain, the patients were characterized as symptomatic (6 patients) and asymptomatic (10 patients).

Symptomatic Patients: (Table I)

Back pain associated with sacroiliac tenderness to palpation was a presenting symptom in one patient (SLE), and it appeared later in the disease in five patients (1 MCTD, 4 SLE). All the patients were white (age 41-57) and were on various steroid regimens. Radiographically, 4 patients had bilateral sacroiliitis (erosions or sclerosis without obliteration), and 1 patient had only right sacroiliitis (ankylosis). Two of these patients (1 bilateral and 1 unilateral) also had aseptic bone necrosis of other joints (hip, knee, ankle). In the sixth symptomatic patient, the sclerosis was limited to the iliac side of the joint, resembling osteitis condensans ilii. HLA-B27 was absent in two of the patients with bilateral sacroiliitis.

TABLE I

Total number of patients = 16	Normal S-I joints	Unilateral sacroiliitis	Bilateral sacroiliitis	Osteitis condensans ilii	Aseptic bone necrosis of other joints	
Symptomatic patients = 6	0	1	4	1	2	
Asymptomatic patients = 10	5	3	0	2	1	

^{*}From the Division of Rheumatology-Immunology, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia

Asymptomatic Patients: (Table I)

Three patients with SLE (2 white, 1 black) had radiographic evidence of unilateral sacroilitis (asymmetric erosions and sclerosis). One of these also had evidence of aseptic bone necrosis of the hip. Five patients had normal sacroiliac joints. Two additional white SLE patients had unilateral sacroiliac joint sclerosis with the iliac side sclerosed to a greater degree than the sacral side.

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Discussion

Definite evidence of sacroiliitis was present in eight patients (50%). Sacroiliitis was present bilaterally in 4 patients (25%), and unilaterally in 4 (25%). Three patients had osteitis condensans ilii. Bilateral involvement was consistently associated with back pain, and in one patient was the presenting symptom. All except two of the affected patients were Caucasian, without any distinctive clinical or serologic features. In three patients sacroiliitis was associated with radiographic evidence of aseptic bone necrosis of other joints.

With an incidence of AS in the general population of 1:71, and an incidence of SLE of 1:1970, the predicted concurrent rate for the two diseases is 1:139,800.^{4, 5} These statistics suggest a rare combination of the two conditions. Epidemiologically these conditions occur in different population groups. Indeed, there are only 4 reported cases of simultaneous SLE and AS.^{6, 7} In our subjects, who represented a relatively homogeneous group as far as sex and socio-economic status, the observed frequency of sacroiliitis coexisting with SLE exceeded by far the expected one.

Genetic and physical influences are speculated in the occurrence of both conditions. Disease expression in both SLE and spondyloarthritis is influenced by histocompatibility antigens. Increased frequencies of HLA-A 1, B 8, DR 2, DR 3,8 and BW 409 have been reported in patients with SLE compared with controls. In addition, HLA-B27 antigen is strongly associated with spondyloarthritis.4 Negative B27 antigen patients with AS have an increased incidence of B7-GREC antigen (B7, Bw22, B40, Bw16), and this public antigen seems to be more important than the B27 in indicating a predisposition to AS.¹²

An increased susceptibility to both conditions in male patients possessing HLA-B 27 or B7-GREG antigens is conceivable through the existence of linkage disequilibrium of A1, B8, DR3, with A3, B7, DR2.¹³

Aseptic bone necrosis is not an uncommon radiologic finding in SLE with or without steroid treatment, and sacroiliac joints may also be affected.¹⁴ Three of the patients with sacroiliitis had evidence of aseptic bone necrosis elsewhere. The possibility of aseptic sacroiliac joint necrosis with secondary degeneration is another possible explanation.

The poorly recognized association of sacroiliitis and SLE may be attributed to the fact that SLE, with its potential fatal manifestations, deters the physicians from further pursuing diagnostically the complaints of back pain, thus underestimating the presence of sacroiliitis. Further studies are needed to confirm our findings on the association between SLE and sacroiliitis and to elucidate the pathogenecity and the significance of this association.

Summary: Eight of our sixteen male SLE and MCTD patients had radiologic evidence of sacroiliitis. This was present most frequently in Caucasians. Of these, five were symptomatic. Three of the patients with radiographic evidence of sacroiliitis had evidence of aseptic necrosis of bone of other joints.

Although genetic predisposition by sharing common histocompatibility antigens or close linkage disequilibrium

is an attractive hypothesis, aseptic bone necrosis of the sacroliac joint is another possible explanation.

Resumen: Cincuenta porciento de nuestros pacientes varones con lupus sistémico eritematoso y enfermedad mixta del tejido conectivo presentaron evidencia radiológica de sacroileitis. Esto fue más común en miembros de la raza caucásica donde notamos una relación entre envolvimiento bilateral articular y necrosis osea aséptica en otros lugares.

Aunque la predisposición genética es muy probable por uno de dos mecanismos; 1) antígenos comunes en el sistema de histocompatibilidad, 2) desequilibrio en enlaces cercanos; la necrosis aséptica osea de estas articulaciones es otra posibilidad.

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Intentos Suicidas en Adolescentes

J. Arturo Sánchez Lacay, M.D. Carmen E. Parrilla Cruz, Ph. D Annette L. Pagán Castro, M.D.

Los autores estudiaron los intentos suicidas Resumen: en adolescentes de 13 a 18 años. Fueron 41 casos de los 203 adolescentes atendidos en 18 meses en la Clínica de Salud Mental del Hospital Pediátrico Universitario. Esto constituyó el 20% de los adolescentes. Se estudiaron las variables edad, sexo o escolaridad, religión, número de intentos, sintomatología, metodología, motivación, composición familiar, posición ordinal, e historial de enfermedad mental en la familia, stresses de vida. Entre los hallazgos más importantes los adolescentes del sexo femenino intentan más que los varones. La sintomatología más frecuente se manifiestan con los problemas relacionados con el afecto. La metodología más usada fueron los medicamentos y las motivaciones detrás de los intentos fueron problemas con los padres. Un alto por ciento de estos intentos fue solo, planificado y no avisado. Los estressores de vida de estos adolescentes fluctuaron entre moderados y severos.

El suicidio es considerado un mal de todos los tiempos y se da en cualquier lugar del mundo, entre personas de todas las edades, sin discrimen por sexo, por creencia religiosa ni por origen de clase. Es un fenómeno social y un problema médico de envergadura.

El suidicio es la décima causa de muerte en todas las edades y la segunda causa de muerte entre los adolescentes en los Estados Unidos.

Hay una tendencia general a consumarse más en varones y a intentarse más entre mujeres.

Se entiende por intento todo acto realizado en el propósito de hacerse daño serio y/o quitarse la vida. El intento es una fase dentro del espectro del comportamiento suicida (idea, amenaza, intento, suicidio consumado).

Según datos de la Oficina Nacional de Censo en Washington D.C. (1978), la proporción de mortalidad es diez veces más alta para el adolescente en un 7.9% en relación a las muertes en los niños.

Jacobziner,¹ Toolan,² y Garfinkel³ coinciden en concluir que el comportamiento suicida aumenta con la edad y en la pubertad.

El suicidio quizás no representa preocupación para la sociedad puertorriqueña por el desconocimiento general sobre el fenómeno suicida, la ausencia de estadísticas confiables y la escasez de investigación sobre el tema.

La Revisión de Puerto Rico (El Mundo, 21 de agosto 1983 9A) informa que para 1982 hubo 14 muertes por suicidio en jóvenes de 10 a 19 años. Esto ha ido incrementándose durante los últimos años. El comportamiento

suicida, los factores precipitantes y los métodos son aspectos que no han sido estudiados en Puerto Rico.

El comportamiento suicida que exhibe el adolescente es de particular interés científico precisamente por la etapa de desarrollo donde se produce. La adolescencia es un estado crítico, un período de transición.

Kurt Glaser, 4, 5, 6, 7 describe al adolescente que exhibe comportamiento suicida como aquel que presenta sentimientos de culpa, sentimientos de no ser querido, desesperanza, depresión, disturbios emocionales y pobre ejecutoria académica.

La depresión ocupa un lugar destacado entre las variables del comportamiento suicida. En la adolescencia es más complicada su detección por la diversidad de manifestaciones que adquiere. Se identifican cambios en el comportamiento general, aislamiento social, cambios de estado de ánimo, disturbios en el sueño (pesadillas e insomnio, agresividad, falta de ánimo, anorexia, ausentismo y fobia escolar.

Toolan,^{8, 9, 10} indica la aparición de alucinaciones, delirios, manipulación y reacciones esquizofrénicas. Mientras Bender y Schilder¹¹ encuentran sentimientos de coraje y deseos de venganza como parte importante del cuadro clínico.

Gould¹² hace énfasis en la depresión como síntoma cardinal en el comportamiento suicida aún cuando entiende que representa un esfuerzo para resolver tensiones o conflictos.

Otros aspectos del cuadro clínico son sentimientos de fracaso, culpa por la ausencia o pérdida de un padre, culpa ante impulsos sexuales, ausencia de protección, hipersensibilidad, pensamiento mágico y la pérdida del objeto amado.

Las variables intervinientes en el comportamiento suicida del adolescente son de índole multifactorial.

Según Lloyd¹³ hay factores predisponentes y factores precipitantes que pueden ser deíndole individual, social y cultural.

Entre los factores individuales están aquellos denominados intrapsíquicos donde ejerce gran influencia la condición emocional y afectiva del suicida. Además, están la dependencia, la culpa, la depresión, sentimientos de rechazo, abandono y minusvalía. Se condideran también las actitudes y las fantasías del adolescente respecto a la muerte y al acto de morir. Los factores sociales son, entre otros, los roles que deben desempeñar, las expectativas que deben llenar, las reglas y normas que deben conocer y saber poner en práctica. Los factores culturales son aquellos que señalan las formas y las maneras de cumplir con las expectativas, lo permitido y lo prohibido por la cultura.

Klagsbrun, 14 señala que la mayoría de los adolescentes

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que intentan quitarse la vida, lo hacen como resultado de una depresión devastadora.

Cualquier etapa del comportamiento suicida en el adolescente puede estar motivado por problemas de relación interpersonal con los padres¹⁵ con los hermanos,¹⁶ los amigos,¹⁷ los novios, por el impacto que sobre él tiene la familia,¹⁸ y la escuela.¹⁹

Jacobs²⁰ identifica historial de problema entre padres e hijos, aislamiento del adolescente durante el cual se intensifica el problema de relación con los padres, intento por parte del adolescente por solucionar o resolver esos conflictos. Finalmente se ejecuta el intento suicida como la solución a esa situación insoportable.

Teicher y Jacobs encontraron que el adolescente suicida está más expuesto a separaciones inesperadas. En el 72% de sus casos estudiados hay un padre o madre ausente por separación, divorcio o muerte.

Morrison y Collier²¹ plantean que el intento suicida del adolescente es sintomático de problemas familiares serios y de larga duración.

Pfeffer²² encuentra que el comportamiento suicida de los padres tiene un efecto definitivo en los niños.

Otra fuente de presión para el adolescente es el sistema escolar²³ como ejemplo dramático están los estudios realizados por Mamoru Iga²⁴ en Japón. El sistema educativo japonés tiene unas demandas en términos de tiempo y calidad de estudio y es un sistema evaluativo de tal magnitud que se identifica como la causa más importante de presión entre los adolescentes japoneses.

La metodología del intento suicida en adolescentes es heterogénea. Varios investigadores, ²⁷, ²⁸ señalan que los varones tienden a usar métodos de acción rápida, métodos violentos que dejen poco margen de sobrevivencia o intervención. Entre los cuales están el ahorcamiento y el lanzarse de lugares altos junto con la ingesta de tóxicos mezclados con alcohol o drogas. Los métodos utilizados por las hembras tienden a ser de acción lenta como tomar medicamentos dando así margen a la intervención o al rescate.

La metodología está vinculada a los patrones prevalecientes en la cultura. Cientos de informes aparecidos en la prensa de Puerto Rico desde 1913 señalan las muertes por suicidio entre adolescentes utilizando e ahorcamiento, las armas de fuego y la ingesta de tóxicos. Para el año 1981 se suicidaron 15 adolescentes (5% del total de suicidios) entre las edades de 15 a 19 años.

La metodología utilizada fue de ahorcamiento - 66.6% (mayormente por varones), ingesta de medicamentos y tóxicos (20.0%) y armas de fuego (13.3%) que fue uso exclusivo de las hembras.

Intimamente relacionado con el comportamiento suicida está el concepto de muerte que tiene el adolescente. Hogan²⁹ encontró en su estudio que los adolescentes suicidas tienen una conceptualización realista de la muerte como cesación definitiva de las actividades corporales. El concepto de muerte se observa de forma clara y definitiva con mayor frecuencia entre los adolescentes con depresión severa.

Definiciones Funcionales

Edad - años cumplidos al momento de solicitar los servicios, 13-18.

Escolaridad - grado que cursa al momento de la entrevista.

Intento - todo acto realizado con el propósito de hacerse daño serio y/o quitarse la vida.

Sintomatología - manifestaciones clínicas que preceden y/o continuan a la aparición del comportamiento suicida.

Motivación - razón que manifiesta el adolescente para explicar su comportamiento.

Composición Familiar - conjunto de datos que incluyen grupo de personas que integran la familia (número de miembros, relaciones entre padres, historial de enfermedad física o mental, historial de suicidio, posición ordinal.

"Stressors" de Vida - presiones ejercidas sobre el adolescente que pueden ser de índole individual, social y cultural.

Concepto de muerte - percepción que tiene el adolescente de la terminación de la vida mediante pruebas proyectivas.

Diagnóstico - proceso de identificar un desórden mental (DSM-III).

Objetivo

Describir los adolescentes entre las edades de 13 a 18 años que presentan un comportamiento suicida manifestado por intento.

Métodos

De abril de 1982 a septiembre de 1983 fueron atendidos en la Clínica de Niños y Adolescentes de Salud Mental, Hospital Pediátrico Universitario, Centro Médico de Puerto Rico, 203 adolescentes entre las edades de 13 a 18 años. Cuarenta y uno de los cuales fueron por intento suicida. La muestra tiene un 100% de representatividad. Se realizaron entrevistas estructuradas a los 41 adolescentes y evaluaciones psiquiátricas y psicológicas tanto al adolescente como a su familia. Las pruebas psicológicas y psicométricas utilizadas fueron: WISC, EIWA, para niños, Dibujo de la Persona, Dibujo de la Familia y el Rorscharch.

Se utilizaron categorías descriptivas en términos de sexo, edad, escolaridad, ubicación, religión, fuente de referido, número de intentos, sintomatología, metodología, motivación, composición familiar (posición ordinal en la familia, historial de enfermedad mental, stresses de vida).

Resultados del Estudio

En la clínica de niños y adolescentes de la Secretaría Auxiliar de Salud Mental se atendieron un total de 1362 niños y adolescentes entre abril de 1982 a septiembre de 1983.

203 son de 13-18 años, de los cuales 41 fueron intentos suicidas.

El 12% de los adolescentes atendidos fueron por intento suicida.

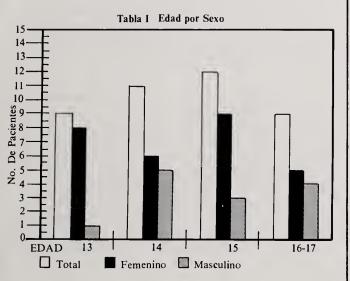
Uno de cada 8 adolescentes que va a la clínica es por intento suicida.

De los 41 adolescentes atendidos 28 son del sexo femenino (68%) y 13 del sexo masculino (32%).

La edad crítica donde aparece el mayor por ciento es a los 15 años (29%), seguidos de los 14 años con un 72%.

La mayor parte de las niñas tienen 15 años seguidas de la edad de 13 años.

La mayor parte de los varones tiene 14 años, seguidos de un grupo de 16 años. Como lo ilustra la tabla número I.



A mayor edad se evidenció un mayor atraso académico.

En general, los adolescentes participantes en el estudio no están en el grupo que corresponde.

Un 32% de las fuentes de referido lo fue el Hospital Universitario de Niños del Centro Médico de Río Piedras, seguidos del Hospital Regional de Bayamón y de la escuela con un 10% cada año.

Un 8% provino de los Centros de Salud Mental y del Hospital Universitario de Adultos del Centro Médico de Río Piedras.

El Departamento de Servicios Sociales refirió pacientes en un 5%, al igual que el Hospital de Psiquiatría de Río Piedras.

Para la sintomatología se establecieron las siguientes categorías para fines de estudio: manifestaciones relacionadas con el afecto, problemas de comportamiento y quejas somáticas, disturbios del pensamiento, disturbios perceptuales y otros, como se evidencia en la Tabla II. El 42% presentó sintomas relacionados con el afecto, seguidos de un 22% que presentó problemas del comportamiento. Un 12% presentó disturbios perceptuales y de pensamiento.

Tanto los varones como las niñas presentaron mayormente sintomatología relacionada con el afecto, seguidos de quejas somáticas. Los varones presentaron en la misma proporción las quejas somáticas y los problemas del comportamiento.

La metodología del intento suicida entre los adolescentes de este estudio fueron el tomar medicamentos en un 68%. En menor proporción le siguen saltar de un piso

Tabla II Sintomatología

Manifestaciones Relacionadas con Afecto

Ansiedad Luto Prolongado
Agresividad Miedos Nocturnos
Coraje Mutismo
Depresión Soledad
Inquietud Tristeza, Llanto

Manifestaciones Somáticas

Anorexia Perdida del Peso
Cansancio Problemas del Sueño
Dolor de Cabeza Dolores Estomacales
Mareos

Problemas de Comportamiento

Maltrato Huir del Hogar
Ausentismo Escolar Problemas con Suegros
Dificultades Maritales Problemas EscolaresPeleas Aprovechamiento

Trastornos Perceptuales y del Pensamiento

alto, tirarse de un carro en movimiento y cortarse.

Entre los medicamentos más utilizados están los analgésicos, los ansiolíticos y los neurolépticos.

Las tres motivaciones más importantes expresadas por los adolescentes con intento suicida fueron: problemas con la familia, en especial con los padres, en un 46%, seguido de deseos de matarse, en un 31% y de problemas con los novios en un 14%.

Los problemas con la familia ocurrieron como mayor fuente de motivación para los adolescentes suicidas de este estudio.

El 54% de los adolescentes estudiados tuvo un intento suicida, un 24% tuvo 2 intentos suicidas; el 15% tuvo tres intentos suicidas y un 7% tuvo de 4 a 8 intentos.

El mayor número de intentos suicidas ocurrió estando el adolescente solo. Fueron intentos planificados, no impulsivos y no avisaron. Ocurrieron mayormente en horas de la noche.

Un 54% de los adolescentes ocupan una posición intermedia en la familia, seguido por un 26% que es el hijo mayor. Un 11% representa el hijo menor y un 9% es el hijo único.

El grupo mayor de padres está separado y/o divorciado en un 42%, seguidos de los que no informan en un 26% y los viudos con un 18%. Solamente un 13% de las parejas aparece como casados.

El 43% de los adolescentes es de religión católica. El 11% son evangélicos, mientras que un 8% son pentecostales. Un 5.4% son de la religión MITA y un 27% no informa.

Un 40% de los adolescentes presentó stresses de vida moderados, mientras que un 30% presentó stresses de vida severos. Es decir, un 70% de los adolescentes de este estudio presentó stresses de vida moderado y severo (Tabla III).

Es significativo señalar que a mayor severidad del estressor de vida, mayor fue el número de intentos. $X^2 = 1.14$; P 0.5 (Tabla IV).

Tabla III Stresses de Vida

LEVE

Pocas actividades recreativas Hacimiento Dificultades con maestros

MODERADO

Peleas frecuentes de los padres
Dificultades académicas
Separación de padres
Nacimiento de hermanos
Problemas económicos
Enfermedades físicas
Múltiples uniones de la madre
Padre o hermanos alcohólicos o adicto
Intervenciones quirúrgicas
Agresión física entre padres
Problemas de aprendizaje

GRAVE

Madre prostituta
Asesinato familiar cercano (tío)
Abandono madre
Padre en la cárcel
Intento de seducción
Embarazo
Muerte padre
Matrimonio
Divorcio
Muerte Abuela

CATASTROFICO

Muertes múltiples (madre y hermano) Violación

Tabla IV	Stresses	de	Vida vs	Número	đе	Intentos
I A DIA I V	2011 62262	uc	viua vs.	Numero	uc	THICHIOS

STRESSES DE VIDA	Pacientes	1 Intento	2 Intentos	3 Intentos
Mínimo-Leve	6	5	0	001
Moderado	15	8	5	002
Severo-Grave Catastrófico	20	9	6	05
Totales	41	22	11	08
$X^2 = 1.14$	P>0.5			

Un 57% de los padres está desempleado distribuyéndose el resto en menor proporción entre operarios, empleos de servicio, pensionados y profesionales.

En un 19% la madre había intentado suicidarse, seguido por un 15% donde las tías maternas habían intentado suicidio.

En cuanto al historial de enfermedad mental en la familia un 31% presentó desórdenes afectivos, seguido de un 26% con padres con abuso de sustancias. En un 16% se encontraron desórdenes mentales con psicosis sin clasificar.

Los adolescentes constituyen un gran por ciento de la población en Puerto Rico; sin embargo los servicios médicos, psicológicos y educativos que enfoquen los problemas particulares de esta etapa de desarrollo son muy limitados.

Los intentos suicidas constituyen un problema serio entre los adolescentes que llegan a los servicios de Salud Mental en Puerto Rico. Uno de cada 8 en este estudio presenta este tipo de conducta.

Entendemos el comportamiento suicida que se manifiesta por ideas, amenazas e intentos como un fenómeno mucho más frecuente de lo que se cree. Lamentablemente no se está detectando de forma adecuada en la población en general.

Consideramos que el estudio del comportamiento suicida es esencial ya que por un lado, cada idea, amenaza e intento es un pedido de ayuda y siempre debe tomarse en serio; por otro lado, los indicadores del comportamiento suicida facilitan el diseño de técnicas de diagnóstico, de intervención a niveles terapeúticos y provee para la educación y adiestramiento de los profesionales de salud mental y de ciencias de la conducta.

El impacto que sufre la familia puertorriqueña en términos sociales, económicos y culturales en nuestra sociedad se traduce en estress y se manifiesta como síntoma en uno de los miembros más vulnerables del sistema familia: el adolescente.

Summary: The authors investigated suicidal attempts in 13 to 18 year old adolescents. Forty one cases out of 203 seen at the Mental Health Clinic in an eighteen month period attempted suicide. The following variables were studied: age, sex, schooling, symptomatology, methods, motivation, family system, psychological stressor and family history of mental illness.

It was found that girls attempted suicide in greater proportion. Symptoms related to affect were prominent. The preferred method were medications. Difficulties with parents motivated most of the suicidal attempts. They were significantly related to psychosocial stressors classified from moderate to severe. Most suicidal attempts were planned, without warning and when the adolescents were alone.

Reconocimiento

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Exposición Humana a Rabia Animal en Puerto Rico, 1980-1983

José G. Rigau-Pérez, M.D., F.A.A.P.* Bernardo J. Marqués-Díaz** Marta E. Benítez-Avila, M.T., A.S.C.P.*** Anthony H. Burton, B.S.****

Resumen: El manejo apropiado de las heridas, y la administración correcta de profilaxis antirrábica son mandatorios para evitar un desenlace mortal en las personas que han sufrido mordeduras por animales. Una alta proporción de mangostas (Herpestes auropunctatus) capturadas en Puerto Rico alberga el virus de rabia. De 1980 a 1983 se encontraron mangostas con rabia en todas las regiones de la isla, y durante todas las estaciones del año. El hallazgo de rabia en perros y gatos ocurrió con mucho menor frecuencia que en las mangostas. Los roedores (ratas, ratones y hamsters) y lagomorfos (conejos y liebres) examinados en el laboratorio fueron todos negativos para rabia. La tasa general de tratamientos antirrábicos en Puerto Rico en 1983 fue 4.77 por cien mil habitantes y el costo de los agentes inmunobiológicos fue de \$60,528. La tasa de tratamiento de varones fue mayor que la de mujeres (6.15 vs. 3.46 por cien mil habitantes). El manejo apropiado de mordeduras por animales se resume con el acróstico RATAS (R-abia, A-ntibióticos, T-étanos, AS-epsia). Para cada víctima de una mordedura hay que considerar la necesidad de profilaxis contra rabia; la necesidad de antibióticos para tratar heridas infectadas, sucias, o severas; la necesidad de inyectarle al paciente antitoxina o inmunoglobulina antitetánica; y la utilidad de limpiar la herida con jabón o desinfectantes.

Prevenir la rabia humana es uno de los servicios que de forma más apremiante exige el público al Departamento de Salud de Puerto Rico. Aunque sólo se ha documentado un caso de rabia humana en la isla en todo este siglo, es necesario gastar miles de dólares en medicamentos cada año para frustar el efecto de mordeduras de animales potencialmente rabiosos. El propósito de este artículo es presentar la información disponible sobre la rabia en animales en Puerto Rico y la exposición humana a animales potencialmente rabiosos.

La rabia es una encefalitis viral de progreso rápido y desenlace mortal. No hay para sus víctimas cura conocida ni aún remedios paliativos. Ocurre en animales de sangre caliente (mayormente los mamíferos) y se trasmite a los humanos por la mordedura de un animal rabioso, contacto con la saliva o tejido del sistema nervioso central del animal, o, rara vez, por inhalación de aerosol con el virus.² La única manera de evitar las muertes por rabia es mediante la prevención: evitar las mordeduras de animales rabiosos y, en las personas mordidas, evitar el desarrollo de la enfermedad mediante la profilaxis antirrábica. Hay disponible también profilaxis pre-exposición, para las personas que por su trabajo se exponen con frecuencia a animales rabiosos.

La prevención de hidrofobia (rabia) en animales se incorporó a los reglamentos de salud pública en Puerto Rico por primera vez en 1841.3 De 1929 a 1949 sólo se documentó un caso de rabia animal (en 1933). A pesar de que el número total de animales examinados en ese período fue muy pequeño, se pensó que la isla estaba libre de rabia. La investigación de un brote de rabia animal en el barrio Monacillos de Río Piedras en 1950 sugirió que el elemento común a todos los animales infectados era haber peleado con mangostas, desde dos semanas hasta dos meses antes del comienzo de los síntomas. La inoculación experimental de rabia en mangostas demostró que éstas podían adquirir la enfermedad. La detección de virus de rabia en dos mangostas salvajes capturadas en Fort Buchanan (área de Guaynabo y Bayamón) en 1950 confirmó que las mangostas estaban sirviendo de reservorio para la rabia en Puerto Rico.4

La mangosta (Herpestes auropunctatus) es un mamífero carnívoro, de la familia Viverridae.5 Se le llama vulgarmente "ardilla", "mangüí" (en Moca e Isabela), o "rata" (en San Sebastián), apelativo que puede causar una confusión peligrosa con la especie Rattus. La mangosta fue traída a Puerto Rico desde Jamaica en 1877 como agente biológico para controlar la población de ratas en los cañaverales. El proyecto no resultó efectivo, pues las ratas son animales nocturnos y las mangostas demuestran su actividad durante el día. Un estudio llevado a cabo en Puerto Rico de 1951 a 1952, capturando mangostas en jaulas dispuestas en varias regiones de la isla, encontró que el ambiente predilecto de estos animales era el de los matorrales espesos, con yerbas de dos a siete pies de altura, cerca de quebradas en las llanuras. Allí la densidad poblacional de mangostas llegaba hasta un animal por acre (1 acre = 1.0297 cuerdas). Las mangostas se alimentaban mayormente de insectos y reptiles y tenían un campo de acción ("home range") con diámetro de 100 a 700 pies. Los únicos ambientes ecológicos de la isla donde no se encontraron mangostas fueron los bosques y las áreas urbanas.6 No hay información más reciente sobre la distribución y el

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comportamiento de la mangosta en el Puerto Rico contemporáneo, tanto más pavimentado que el de 1951. Proyectos de erradicación de las mangostas en otras islas del Caribe no han acertado con la forma de eliminar este reservorio de la rabia. No hay estudios que expliquen si la trasmisión de la rabia entre las mangostas se mantiene por trasmisión trasplacental o mediante el contagio por mordeduras o saliva. Las mangostas rabiosas son agresivas y muerden otros animales aun de mayor tamaño que ellas. De esta forma pasa el virus a perros, gatos y ganado, y de ahí al ser humano.

Métodos

La información sobre rabia en animales desde enero de 1980 hasta diciembre de 1983 se obtuvo de los informes mensuales del Laboratorio de Virología del Instituto de Laboratorios del Departamento de Salud. El Laboratorio procesa todas las muestras que le son enviadas de Puerto Rico e Islas Vírgenes, y diagnostica rabia con el examen de tejido nervioso por inmunofluorescencia directa.8, 9 La información para Islas Vírgenes no fue incluída en este estudio. Los datos del Laboratorio se analizaron con un microcomputador y el Sistema de Análisis Epidemiológico, programa en idioma "Basic" desarrollado por uno de los autores (AHB). Los informes mensuales del Laboratorio desglosan la información por municipio, y tres municipios deben ser considerados de manera especial. En Guaynabo esté el Refugio de animales de la "Humane Society of Puerto Rico, Inc.", que envía al Laboratorio animales que proceden de otros pueblos cercanos. A Cataño y Ceiba se asignan los animales procedentes de las bases militares de Buchanan y Roosevelt Roads, respectivamente, donde hay programas para atrapar mangostas, como medida rutinaria de control de plagas. El porciento mensual de positividad para rabia se analizó sólo para mangostas y perros, por haber muy pocos casos positivos de los otros animales cada año. Se asignó cada pueblo a la región climática a que pertenece según la clasificación del Servicio Forestal.¹⁰

La información sobre tratamientos para personas expuestas a animales potencialmente rabiosos en 1983 se obtuvo de las hojas de requisición de vacuna y suero antirrábico del Programa de Inmunización del Departamento de Salud. Para verificar la exhaustividad del expediente, se obtuvo de Merieux Institute, Inc. (Miami, Florida), único distribuidor de vacuna antirrábica en Puerto Rico en 1983, la lista de clientes en ese año. Se encontraron así diez casos, cuyas hojas de requisición habían sido archivadas en la Región de Ponce. Las hojas de requisición habían sido archivadas en la Región de Ponce. Las hojas de requisición proveen información sobre las siguientes características de cada caso: nombre, edad, sexo, dirección residencial, fecha en que ocurrió la exposición, animal que ocasionó la exposición al paciente, circunstancias de la mordedura, tratamiento de la herida, y datos sobre el comportamiento del animal. Las hojas fueron cumplimentadas por médicos, enfermeras o secretarias del lugar que solicitaba los medicamentos para el paciente. Distintos formularios usados en 1983 solicitaban diferente información, y la cantidad de información en las hojas es muy variable. Los casos tabulados

aquí no incluyen las personas tratadas en bases militares o en el Hospital de Veteranos, ni las personas que recibieron tratamiento antirrábico pre-exposición o refuerzos de tratamiento pre-exposición porque su profesión los expone a animales enfermos. El Departamento de Salud no provee vacuna contra rabia en esas circunstancias. La información sobre el lugar de residencia se categorizó por Región administrativa del Departamento de Salud (ver tabla I. Los datos poblacionales utilizados para calcular tasas por Región de residencia, sexo y edad se refieren a 1982, años más reciente para el cual contamos con un estimado detallado de la población.¹¹

Tabla I

Pueblos Comprendidos en las Regiones y Subregiones Administrativas del Departamento de Salud de Puerto Rico en 1983.

METROPOLITANA	BAYAMON	ARECIBO
Canóvanas	Barranquitas	Arecibo
Carolina	Bayamón	Barceloneta
Guaynabo	Cataño	Camuy
Loíza	Comerío	Ciales
San Juan	Corozal	Florida
Trujillo Alto	Dorado	Hatillo
	Naranjito	Lares
	Orocovis	Manatí
	Toa Alta	Morovis
	Toa Baja	Quebradillas
	Vega Alta	Utuado
		Vega Baja
FAJARDO	CAGUAS	PONCE
Ceiba	Aguas Buenas	Adjuntas
Culebra	Aibonito	Arroyo
Fajardo	Caguas	Coamo
Luquillo	Cayey	Guánica
Río Grande	Cidra	Guayama
Vieques	Gurabo	Guayanilla
	Humacao	Jayuya
	Juncos	Juana Díaz
	Las Piedras	Patillas
	Maunabo	Peñuelas
	Naguabo	Ponce
	San Lorenzo	Salinas
	Yabucoa	Santa Isabel
		Villalba
		Yauco
MAYAGUEZ	AGUADILLA	
Añasco	Aguada	
Cabo Rojo	Aguadilla	
Hormigueros	Isabela	
Lajas	Moca	
Las Marías	San Sebastián	
Maricao		
Mayaguez		
Rincón		
Sabana Grande		
San Germán		

Resultados

Rabia animal

De 1980 a 1983 sólo cuatro municipios no enviaron al Laboratorio ningún animal para examen: Adjuntas, Culebra, Sabana Grande y Utuado. El laboratorio examinó un total de 1,136 especímenes, para un promedio anual de 284 y mensual de 24 animales. Se encontraron 286 animales con rabia (25.2%), con un promedio de 72 por año. La tabla II demuestra que el tipo y número de animales examinados, y la proporción de animales que resultaron rabiosos, se mantuvieron casi constantes de 1980 a 1983, excepto por las mangostas capturadas en Cataño y Ceiba.

Durante los cuatro años estudiados, la positividad promedio para rabia en mangostas enviadas al Laboratorio por los municipios, excluyendo a Cataño y Ceiba, fue de 77% (184/239). El promedio general es más bajo (47%) porque el porciento de positividad en Cataño y Ceiba es sólo 15%. La positividad de mangostas por mes, en Ceiba y Cataño varió de 5.3 a 60%. En el resto de los pueblos la positividad fue de 66.7 a 91.7%. En ambas series los meses en que el Laboratorio encontró mayor tasa de positividad fueron octubre y noviembre, pero como los datos no provienen de un sistema estructurado de muestreo de animales, esta aparente tendencia estacional puede ser falsa.

El porciento de positividad para rabia en mangostas recogidas de 1980 a 1983 por las diferentes regiones administrativas del Departamento de Salud (excluyendo Ceiba y Cataño) varió poco: de 69.4% (Región Metropolitana) a 90.3% (Región de Arecibo). Hay que mencionar

en el área de bosque mojado subtropical (Adjuntas, Lares, Las Marías, Maricao y San Sebastián) sólo el último envió mangostas al laboratorio y todas (3/3) fueron positivas para rabia.

Los perros y los gatos examinados en el cuatrenio tuvieron porcientos de positividad de 10% y 7%, respectivamente. La prevalencia mensual de rabia en perros examinados varió de 2.6 a 16.1%, también con máximo en noviembre. La prevalencia por región de Salud fue desde 5% en la Región Metropolitana hasta 27% en la de Arecibo. Diez pueblos (13%) no enviaron ningún perro para examen, y otros 49 (62%) enviaron en promedio menos de un perro al año. Los siete gatos con rabia procedieron de diversos municipios en distintas regiones de la isla (San Juan, Yauco, Isabela, Santa Isabel, Ponce, Yabucoa, y Juana Díaz), en distintos años.

El ganado vacuno con rabia fue todo del norte de la isla (Hatillo, Moca, San Sebastián, Arecibo, Dorado, Toa Baja, Manatí). Los ocho animales con rabia clasificados como "otros animales domésticos" fueron siete caballos (de Bayamón, Dorado, Canóvanas, Carolina, Toa Baja, Yabucoa y Manatí) y una cabra (de Fajardo). Es importante señalar que, como todos los años, los roedores (ratas, ratones y hamsters) y lagomorfos (conejos y liebres) examinados en el laboratorio fueron todos negativos para rabia.

Tabla II

	Pos.1	1980 Exam. ²	%Pos.3	Pos.	1981 Exam.	%Pos.	Pos.	1982 Exam.	%Pos.	Pos.	1983 Exam.	%Pos.	Pos.	Total Exam.	% Pos
Mangostas															
Cataño y Ceiba	4	15	26.67	14	57	24.56	12	130	9.23	5	26	19.23	35	228	15.3
Otros pueblos	53	71	74.65	56	67	83.58	40	57	70.18	35	44	79.55	184	239	76.99
Total	57	86	66.28	70	124	56.45	52	187	27.81	40	70	57.14	219	467	46.90
Perros	6	103	5.83	17	118	14.41	8	109	7.34	10	99	10.10	41	429	9.5
Gatos	2	28	7.14	2	22	9.09	2	28	7.14	1	23	4.35	7	101	6.9
Reses	4	7	57.14	6	9	66.67	0	5	.00	i	3	33.33	11	24	45.8
Otros animales domésticos	2	6	33.33	1	4	25.00	4	8	50.00	1	4	25.00	8	22	36.3
Zorrillos	0	1	.00	0	I	.00		-		0	1	.00	0	3	.0
Mapaches		-			-			-		0	1	.00	0	1	.0
Murciélagos	0	2	.00	0	9	.00	0	3	.00	0	2	.00	0	16	.0
Roedores y lagomorfos	0	21	.00	0	24	.00	0	19	.00	0	9	.00	0	73	.0

^{1.} Pos. = animales con examen positivo para rabia

que 27% (21/78) de los pueblos de la isla no enviaron mangostas para examen, entre ellos siete de los 12 pueblos de la Región de Arecibo. Otros 32 pueblos (41%) enviaron en promedio menos de una mangosta al año. No hay diferencia en la prevalencia de positividad de mangostas en los pueblos de la región climática denominada bosque seco subtropical (74% de positividad) y los de bosque húmedo subtropical (77%). De los cinco pueblos

Exposición humana en 1983

En 1983 se distribuyeron 156 tratamientos por exposición a rabia. Cada tratamiento consiste en la administración de inmunoglobulina humana antirrábica ("rabies immune globulin" - "RIG") y de cinco dosis (a lo largo de un mes) de vacuna antirrábica producida en células humanas diploides ("human diploid cell vaccine" -

^{2.} Exam. = animales examinados para rabia

^{3. %}Pos. = porciento de animales examinados que fueron positivos para rabia

"HDCV"). El tratamiento para una persona de 70 kg de peso cuesta actualmente \$388 (\$20 por mililitro de RIG, \$40 por dosis de vacuna). El costo total mínimo de estos tratamientos fue de \$60,528 sin contar los gastos de almacenamiento, transporte y administración de los inmunobiológicos. El 55% de las exposiciones se debieron a contacto con perros, 32% tuvieron contacto con mangostas, 8% con gatos, 2% con ratas, y 1% cada uno con caballos o murciélagos. En 87.8% (136/156) de los casos la exposición a virus de rabia ocurrió mediante una mordedura. En los 20 casos restantes, ocho tuvieron contacto con la saliva de un mismo perro, dos tocaron la sangre de una mangosta al cortarle la cabeza, uno succionó la herida de otra persona mordida por una mangosta. En 9 casos la exposición no fue claramente definida (dos tuvieron "contacto con perro positivo para rabia", y siete tuvieron "contacto con perro mordido por mangosta"). Hubo un promedio mensual de 12 casos (144/12) y valores extremos de 4 y 19 casos por mes (utilizando los 144 casos con información sobre la fecha de la exposición), sin una clara tendencia estacional para la notificación de casos. La tasa de tratamientos para la isla entera fue de 4.77 por cien mil habitantes. La mayor tasa de tratamientos por Región de residencia se ve en la Región de Caguas (8.31 tratamientos por cien mil habitantes), y la tasa menor (2.08) en la Región de Aguadilla. Las otras regiones tienen las siguientes tasas: Arecibo-6.63, Ponce- 5.45, Fajardo-3.73, Bayamón- 3.52, Metropolitana- 2.75, Mayagüez- 2.56 por cien mil habitantes. Para 8 casos no había información sobre su dirección. La tabla III demuestra la distribución de los casos y las tasas de tratamiento por edad y sexo. Los varones tienen una tasa de tratamiento mayor que la de las mujeres (6.15 vs. 3.46 por cien mil habitantes). El 67% de los casos varones está en los grupos de edad de 5 a 44 años, pero las tasas de exposición son muy parecidas en todos los grupos (menos los infantes, por supuesto), con valores extremos de 3.77 a 8.07 casos por 100,000 habitantes. En las mujeres el 52% de los casos tiene de 5 a 44 años de edad, y las tasas de tratamiento son más variables que para los hombres, de 0.84 a 7.38 casos por cien mil habitantes, con valores altos en las niñas de 1 a 4 años, mujeres adultas (35-54 años) y de 65 años o mayor edad.

Discusión

Estos datos sobre rabia animal en Puerto Rico no se pueden tomar como fiel imagen del problema en la fauna de la isla. Es muy difícil presentar la distribución geográfica de la rabia cuando los especímenes provenientes de cada pueblo son tan escasos. Los animales enviados al laboratorio no son representativos de toda la población de esa especie, ni tampoco de la población de los animales que muerden. Los especímenes que analiza el laboratorio no provienen de un muestreo sistematizado de animales silvestres o realengos, sino de investigaciones de mordeduras o de animales sospechosos. La ausencia de información sobre las personas tratadas en bases militares hace que las tasas de tratamiento aquí presentadas sean más bajas de lo que son en realidad. Por el otro lado, el sistema de asistencia médica y el nivel de preocupación por la rabia son, en las bases militares, muy distintos de lo

que ocurre en el resto de la isla. No más de cinco personas recibieron tratamiento antirrábico post-exposición en el Hospital de Veteranos en 1983 (información del servicio de Farmacia, Hospital de Veteranos).

A pesar de tantas limitaciones, este análisis respalda algunas conclusiones cualitativas, ya que no cuantitativas. Una alta proporción de mangostas capturadas en Puerto Rico alberga el virus de rabia. La tasa de positividad en mangostas capturadas en Buchanan y Roosevelt Roads sugiere que la prevalencia de infección es alta aún en las mangostas que se examinan sin haber causado mordeduras. Se han encontrado mangostas con rabia en todas las regiones de la isla (administrativas o ecológicas) y durante todas las estaciones del año. La ausencia de rabia en roedores de 1980 a 1983 concuerda con la experiencia del laboratorio desde 1950 y respalda la idea de que las mordeduras por roedores acarrean un riesgo mínino para rabia. Los resultados negativos en mapaches y zorrillos (mascotas importadas) y murciélagos no se pueden interpretar de la misma forma, por el número pequeño de especímenes examinados, el precedente en 1977 de un murciélago dudosamente positivo proveniente de la vecina isla de Santa Cruz, y el conocimiento de que todos estos animales son afectados frecuentemente por la rabia en los Estados Unidos continentales. 12 Aunque en Puerto Rico no hay murciélagos vampiros, que son los más comúnmente envueltos en la trasmisión de rabia, se ha documentado en otros lugares del Caribe que los murciélagos frugívoros e insectívoros también pueden trasmitir el virus. 13-15

Los datos sobre exposiciones humanas son de limitada fiabilidad. Su exactitud depende del interés y del tiempo que tenga la persona que los anota. No se recogieron por una misma persona, ni por un mismo tipo de profesional, ni aún en un mismo cuestionario. Para algunas exposiciones no tenemos ninguna información, y para el resto no tenemos algunos datos importantes, como el lugar donde ocurrió la exposición a rabia (que no es necesariamente la residencia del paciente). Como las hojas de requisición de vacuna no se parean rutinariamente con los informes del laboratorio, no se verifica a nivel central la necesidad de continuar cada tratamiento. Por último, con información detallada para sólo un año, es posible que algunos de los hallazgos para 1983 sean la excepción, más que la regla.

Utilizando métodos parecidos a los de este estudio, la tasa de tratamientos antirrábicos en Estados Unidos en 1980-81 se calculó en 4.72 por 100,000 habitantes. 16 Aunque la tasa local de tratamientos en 1983 (4.77 por 100,000 habitantes) es casi idéntica, la similaridad podría ser el resultado de tendencias opuestas, en Estados Unidos y Puerto Rico, en factores no incluídos en los estudios, como por ejemplo la accesibilidad de servicios de emergencia y la percepción del riesgo de rabia por médicos y pacientes. La eficacia de los dos sistemas no puede evaluarse mediante la simple comparación de tasas de tratamiento. No es sorprendente encontrar mayores tasas de tratamiento para hombres que para mujeres, suponiendo que ellos tengan mayor actividad fuera de casa. Pero entonces, ¿cómo explicar que, en mujeres, la mayor tasa de tratamiento se vea entre las señoras de la mayor edad? Quizás tienen mayor acceso a atención

Tabla III

	HOMBRES				HOMBRES MUJERES							TOTAL			
Edad (años)	Casos	%	Población	Tasa	Casos	%	Población	Tasa	Casos	%	Población	Tasa			
1	0	.00	37261	.00	0	.00	36092	.00	0	.00	73353	.00			
1-4	7	7.14	139938	5.00	5	8.62	135171	3.70	12	7.69	275109	4.36			
5-14	20	20.41	348465	5.74	7	12.07	335485	2.09	27	17.31	683950	3.95			
15-24	23	23.47	304466	7.55	8	13.79	319073	2.51	31	19.87	623539	4.97			
25-34	9	9.18	223243	4.03	5	8.62	253335	1.97	14	8.97	476578	2.94			
35-44	14	14.29	173406	8.07	10	17.24	194782	5.13	24	15.38	368188				
45-54	5	5.10	132471	3.77	6	10.34	148635	4.04	11	7.05	281106	6.52			
55-64	6	6.12	110270	5.44	ĭ	1.72	119349	.84	7	4.49		3.91			
65+	7	7.14	122895	5.70	10	17.24	135463	7.38	17	10.90	229619	3.05			
Desconocido	7	7.14	-	-	6	10.34	133403	7.56	13	8.33	258358	6.58			

^{*}Tasas por 100,000 habitantes. Datos de población del Informe anual de estadísticas vitales, 1982.

médica que otros grupos de la población, por su propia iniciativa o por la insistencia de sus familiares; o quizás tienen mayor conciencia de los riesgos inherentes en una mordedura de animal. La información disponible no es suficiente para probar ninguna de estas hipótesis.

El número de personas tratadas para prevenir la rabia varía marcadamente de año en año. En 1980 el Departamento de Salud compró vacuna para 26 tratamientos. En 1981 se suministraron 204 tratamientos, en 1982 fueron 121 y en 1983, como ya se indicó, 156.17 Sin embargo, el número de animales sometidos al Laboratorio, y su positividad para rabia, no ha variado mucho de 1980 a 1983 (tabla II), ni es muy diferente de los datos disponibles para la década 1970-1979. 18 Esta discrepancia entre el aumento en tratamientos y la regularidad de los datos del laboratorio se explicaría por dos situaciones que pueden estar coexistiendo: mayor acceso de los pacientes a los agentes inmunoprofilácticos (es decir, mayor conciencia entre el público y los profesionales de medicina, y mejor distribución de HDCV y RIG), y mayor incidencia de mordeduras (pero sin que se envíen al Laboratorio los animales sospechosos). Sin duda hay menos resistencia al uso de la vacuna desde 1980 pues la HDCV produce reacciones adversas en muy raras ocasiones. 12 Además, sólo tienen que administrarse cinco dosis de HDCV, y no las 23 de la antigua vacuna de embrión de pato. Según las estadísticas del Departamento de Salud, el número notificado de personas mordidas por animales no ha variado de 1980 a 1983 (cerca de 8,000 personas por año).19

La prevención de rabia humana exige dos vías de acción simultánea: evitar la exposición (generalmente por mordeduras) y dar tratamiento adecuado a los pacientes expuestos. Para eliminar la exposición a rabia lo mejor sería erradicar el reservorio del virus. Esto implicaría interrumpir la trasmisión de rabia entre las mangostas o exterminar su población en la isla. No hay evidencia de que programas rutinarios para atrapar o envenenar mamíferos terrestres produzcan, a la larga, esos resultados.²⁰ Hay gran necesidad de un estudio detallado sobre la vida y hábitos de las mangostas en Puerto Rico, y la manera en que adquieren y trasmiten la rabia. También sería muy útil un estudio similar sobre los murciélagos, para determinar si en Puerto Rico son un vector de este virus.¹³ Evidentemente, es indispensable

educar a los ciudadanos sobre la rabia y el riesgo de infección que ofrecen los animales, particularmente las mangostas.

Recomendaciones para el manejo de mordeduras por animales

EL manejo apropiado de mordeduras por animales se resume con el acróstico RATAS (R-abia, A-ntibióticos, T-étanos, AS-epsia). Para cada víctima de una mordedura hay que considerar la necesidad de profilaxis contra rabia; la necesidad de antibióticos para tratar heridas infectadas, sucias, o severas; la necesidad de inyectarle al paciente antitoxina o inmunoglobulina antitetánica (dependiendo de su historial de vacunación y de la condición de la herida); y la utilidad de limpiar la herida con jabón o desinfectantes.²¹⁻²³

Los componentes esenciales de la profilaxis antirrábica son el tratamiento local de la herida, y la inmunización con RIG y HDCV. Todas las mordedura y heridas contaminadas con saliva animal deben ser lavadas escrupulosamente con una solución de iodo-povidone diluída al 1% (la solución usada en cirugía está al 10%, así que hay que diluírla). En heridas con alto riesgo de rabia, la solución desinfectante debe ser cloruro de benzalkonio al 1%, seguida por irrigación copiosa con solución normal salina. La irrigación debe llevarse a cabo con suficiente líquido y presión, y se recomienda usar 250 ml. de líquido (según el tamaño de la herida) con una jeringuilla de 15-20 ml. y una aguja calibre 19. El tejido necrótico debe ser debridado cuidadosamente. Las recomendaciones más recientes señalan la ventaja de suturar las heridas en la cara, torso o extremidades, pero dejar abiertas aquellas con alto riesgo de infección (como lesiones por punción) y las heridas en manos y pies.²³

El uso adecuado de la profilaxis antirrábica es muy importante, porque afecta las dos vertinentes del problema de la rabia: prevenir casos de rabia humana y evitar el uso (y consiguiente gasto) innecesario de los agentes inmunoprofilácticos. A continuación se exponen unas recomendaciones para la prevención de rabia en pacientes mordidos por animales en Puerto Rico. Estas guías acoplan la información disponible sobre rabia animal en la isla y las guías del Servicio de Salud Pública Federal para prevención de rabia, cuya lectura es mandatoria para el profesional de salud responsable de tratar

pacientes que han sufrido mordeduras por animales. 12 La necesidad de tratamiento antirrábico se decide después de conseguir información sobre tres temas: tipo de exposión a rabia, cómo ocurrió la exposición, y qué animal está implicado. La rabia se trasmite por la introducción del virus en cortaduras o heridas de la piel, o por penetración através de las membranas mucosas. El contacto casual con un animal, como pasarle la mano por el lomo (sin que haya mordedura o exposición a saliva o tejido cerebral), no constituye una exposición significativa ni es razón para administrar profilaxis antirrábica. Las exposiciones peligrosas más frecuentes son las mordeduras y los rasguños contaminados con saliva de animal. Otras situaciones, como trasmisión de la rabia por trasplantes de córnea, o respirar virus aerosolizado en laboratorios o cuevas infestadas con murciélagos rabiosos, son extremadamente raras.²

Una descripción detallada del incidente en que ocurrió la exposición ayuda a decidir si la mordedura fue provocada o no provocada. Un ataque no provocado es más indicativo de que un animal está enfermo de rabia, que un ataque provocado. Las mordeduras que ocurren cuando una persona está tratando de alimentar o tocar un animal aparentemente saludable, o al recoger un animal herido, deben considerarse generalmente como provocadas. Todo animal que haya ocasionado una mordedura no provocada debe sacrificarse, y la cabeza (refrigerada, no congelada) enviarse al laboratorio. Haciendo excepción a la regla, si el animal es perro o gato, puede aislarse y mantenerse bajo la vigilancia de un veterinario por diez días.

Al conocer la especie de animal que causó la mordedura se puede juzgar la necesidad de que el paciente reciba profilaxis antirrábica (ver tabla IV). Aunque se recomienda comenzar rápidamente el tratamiento de toda persona mordida por mangosta o por murciélago, es innecesario completarlo si el animal es negativo para rabia en el examen del laboratorio. No hay que comenzar inmediatamente el tratamiento a personas mordidas por cualquier animal (excepto mangostas) si el animal que ocasionó la mordedura va a ser examinado prontamente en el laboratorio. Se debe esperar por ese resultado antes de administrar los agentes inmunobiológicos, a menos que se trate de mordedura por mangosta o que no se haya enviado el animal al laboratorio. Sólo se pueden someter a aislamiento y obsevación los perros o gatos que parezcan estar saludables. Los otros animales potencialmente rabiosos deben ser sacrificados y examinados en el laboratorio, porque no hay suficiente información sobre el desarrollo de la rabia en estos otros animales como para establecer la duración apropiada de su aislamiento.² Las mordeduras por roedores usualmente no ameritan profilaxis antirrábica.²⁴ No es que la rabia sea imposible en los roedores; muchos laboratorios han llevado a cabo importantes investigaciones sobre la rabia mediante la inoculación parentérica del virus en roedores de laboratorio.²⁵ La profilaxis antirrábica para una mordedura de roedor se justifica si el animal implicado resulta positivo en el examen del laboratorio, o, en caso de que el animal no pueda ser capturado, si se observó sumamente agresivo, mordiendo furiosamente sin provocación.

Tabla IV

Guía para Profilaxis Antirrábica Post-exposición en Puerto Rico

Las siguientes recomendaciones son sólo una guía. Al aplicarlas, se debe considerar la especie de animal implicado, las circunstancias de la mordedura u otra exposición, y el historial de vacunación del animal. Se debe consultar a los oficiales de salud pública locales o estatales si hay dudas sobre la necesidad de administrar profilaxis antirrábica.

Especie animal	Condición del animal al momento del ataque	Tratamiento de la persona expuesta*
Perro, gato	Saludable y disponible para 10 días de observación	Ninguno, a menos que el animal desarrolle rabia+
	Rabioso o sospechoso de rabia	RIG y HDCV
	Desconocido (escapó)	Consulte oficiales de salud pública. Si el tratamiento está indicado, dar RIG y HDCV
Mangosta, murciélago	Considerarlo rabioso a menos que se pruebe negativo por laboratorio #	RIG y HDCV
Vacas, caballos, cerdos, cabras, mascotas importadas (ej. zorrillos, mapaches y otro carnívoros)	Consultar oficiales de salu o estatales sobre la necesia antirrábico.	ıd pública locales
Roedores y lagomorfos: ratas, ratones, "hamsters", conejillos de Indias, conejos, liebres, etc.	Como arriba. Las morded casi nunca ameritan profil	

*Todas las mordeduras y heridas deben ser limpiadas escrupulosamente con, por lo menos, agua y jabón. Si el tratamiento antirrábico es indicado, ambos componentes, la inmunoglobulina humana antirrábica ("RIG"), y la vacuna antirrábica producida en células humanas diploides ("HDCV"), deben administrarse lo más pronto posible, sin importar el intervalo transcurrido desde la exposición. Las reacciones locales a las vacunas son comunes y no son razón para suspender el tratamiento. Suspenda la vacunación si las pruebas de anticuerpo fluorescente en el animal son negativas.

+Durante el período usual de vigilancia de 10 días, empiece el tratamiento con RIG y HDCV a la primera seña de rabia en el perro o gato que haya mordido a alguien. El animal sintomático debe ser sacrificado inmediatamente y examinado por el Labortorio de Virología.

#El animal debe ser sacrificado y examinado inmediatamente por el Laboratorio de Virología. No se recomienda que se mantenga bajo observación.

Profilaxis antirrábica

El Programa de Inmunización despacha gratis los agentes inmunobiológicos necesarios para la profilaxis antirrábica, si la requisición está justificada y acompañada de la hoja de investigación de casos posiblemente expuestos a rabia (forma DE#13), y la hoja de requisición

de vacunas. El paciente que necesite profilaxis antirrábica debe recibir RIG en una dosis de 20 Unidades Internacionales por kilogramo, que equivale a 0.06 ml. por libra de peso. Si la anatomía de la parte mordida lo permite, la mitad del volumen calculado de RIG debe infiltrarse alrededor de la mordedura, y el resto se administra en una inyección intramuscular. Cuando no hay RIG, y el paciente empieza a recibir la vacuna antirrábica, se recomienda no administrar RIG si han pasado 8 días después del comienzo de la vacunación con HDCV. Es importante insistir en que los pacientes deben recibir RIG y HDCV para estar adecuadamente protegidos, y que esa protección puede empezarse no importa cuántos días hayan transcurrido desde la mordedura u otra exposición. La vacunación antirrábica consiste en 5 dosis (cada dosis es 1 ml.), administradas por vía intramuscular en el brazo (área deltoide), no en el glúteo.26 Cada dosis corresponde a los días 0 (visita inicial), 3, 7, 14 y 28. Con la vacuna que actualmente se usa, no es necesario hacer pruebas serológicas de confirmación después de la vacunación, a menos que el paciente esté recibiendo (por la razón que sea) agentes inmunosupresores, como por ejemplo corticosteroides. Como con todos los medicamentos y agentes biológicos, hay que tomar en cuenta las contraindicaciones y posibles reacciones adversas de RIG y HDCV. Por las consecuencias graves de una exposición a rabia, y por datos (limitados) que indican que la vacunación contra rabia no ha sido asociada a anormalidades fetales, no hay contraindicación para esta profilaxis durante el embarazo. A las personas con historial de hipersensitividad se las debe vacunar con precaución. Las reacciones adversas a RIG y HDCV han sido muy escasas, excepto por dolor y malestar en el lugar de la inyección, y molestias sistémicas leves como dolor de cabeza, náusea, dolor abdominal o muscular y mareos. Algunas de estas reacciones han ocurrido en 20-25% de las personas tratadas. 12

La evaluación de una exposición a rabia puede ser compleja. El Departamento de Salud ofrece a los médicos consultoría sobre profilaxis antirrábica através de personal con experiencia a nivel local (unidades de salud pública, centros de diagnóstico y tratamiento), regional (enfermeras regionales de epidemiología e inmunización), y central (División de Epidemiología, 758-5422 y 758-5344; Programa de Inmunización, 763-3205; Laboratorio de Virología, 766-1616). De esta forma se estimula una utilización eficaz de los métodos más seguros para la prevención de rabia humana en Puerto Rico.

Abstract: Appropriate wound management, and the correct administration of rabies post-exposure prophylaxis are mandatory to prevent a fatal outcome in persons who have suffered animal bites. A high proportion of mongooses (Herpestes auropunctatus) captured in Puerto Rico are infected with rabies virus. From 1980 to 1983 rabid mongooses were found in all regions of the island, and throughout all seasons. The finding of rabies infection in dogs and cats occurred much less frequently than for mongooses. All laboratory examinations of rodents (rats,

mice, and hamsters) and lagomorphs (rabbits and hares) were negative for rabies. The general rate of administration of rabies postexposure prophylaxis in Puerto Rico in 1983 was 4.77 treatments per hundred thousand population, and the cost of the immunobiologics was \$60,528. The treatment rate was greater for men than for women (6.15 vs. 3.46 per hundred thousand population). The appropriate management of animal bites can be summarized by the mnemonic RATS (R-abies, A-ntibiotics, T-etanus, S-oap). For every animal bite victim, consideration must be given to the need for rabies prophylaxis; the need for antibiotic therapy for infected, dirty or extensive wounds; the need for administering tetanus antitoxin or immuneglobulin; and the need to clean the wound with soap or disinfectants.

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In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at a cause and an appear to the pretreatment of the heart at a cause and an appear to the pretreatment of the heart at the pretreatment.

In angina pectors, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work canacity.

pressure and systolic ejection period in the riet physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity. In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain. The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain. Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved in the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

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INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated in the inariagement of patients with angina pectoris.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

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CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

INDEHAL WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—
PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholarime stimulation of beta receptors MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the hoard is exceeded. Apresthese characteristic and the production of the product

the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures



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INDERAL (propranolol HCI), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the ap-

DIABLIES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the ap-pearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests. IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

lead to a fetum of introfeased intradcular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpines should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug. Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman. Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy. Cardiovascular bradycardia, congestive heart failure, intensification of AV block, hypotension; paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System lightheadedness, mental depression manifested by insomnia, lassitude, weakness, flatigue; reversible mental depression progressing to catationia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrontestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea,

Hematologic agranulocytosis, nonthrombocytopenic purpura thrombocytopenic purpura Auto-Immune In extremely rare instances, systemic lupus erythematosus has been

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practiolo) have not been associated with progranolol DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolof hydrochloride in a sustained-release capsule for administration once daily if patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval HYPERTENSION—Dosage must be individualized. The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily in some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—Dosage must be individualized. Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily in angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established. If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

If treatment is to be discontinued, each of the initial oral dose is 80 mg INDERAL LA MIGRAINE—Dosage must be individualized. The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose. INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

Should be discontinued in that seems several weeks
HYPERTROPHIC SUBAORTIC STENOS/S—80-160 mg INDERAL LA once daily
PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

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ARTICULOS ESPECIALES

Lowering Blood Cholesterol to Prevent Heart Disease*

oronary heart disease is responsible for more than 550,000 deaths in the United States each year. It is responsible for more deaths than all forms of cancer combined. There are over 5.4 million Americans with symptomatic coronary heart disease and a large number of others with undiagnosed coronary disease, many of them young and highly productive. It has been estimated that coronary heart disease costs the United States over \$60 billion a year in direct and indirect costs.

Coronary heart disease is due to atherosclerosis, a slowly progressive disease of the large arteries that begins early in life but rarely produces symptoms until middle age. Often the disease goes undetected until the time of the first heart attack, and this first heart attack is often fatal. Modern methods of treatment have improved greatly the outlook for patients having heart attacks, but major progress in our battle against this number one killer must rest on finding preventive measures.

A number of risk factors have been identified as strongly associated with coronary heart disease. Cigarette smoking, high blood pressure, and high blood cholesterol are the most clearly established of these factors. Risk is greater in men, increases with age, and has a strong genetic component. Obesity, diabetes mellitus, physical inactivity, and behavior pattern are also risk factors.

A large body of evidence of many kinds links elevated blood cholesterol levels to coronary heart disease. However, some doubt remains about the strength of the evidence for a cause-and-effect relationship. Questions remain regarding the exact relationship between blood cholesterol and heart attacks and the steps that should be taken to diagnose and treat elevated blood cholesterol levels.

To resolve some of these questions, the National Heart, Lung, and Blood Institute and the NIH Office of Medical Applications of Research convened a Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease on December 10-12, 1984. After hearing a series of expert presentations and reviewing all of the available data, a consensus panel of lipoprotein experts, cardiologists, primary care physicians, epidemiologists, biomedical scientists, biostatisticians, experts in preventive medicine, and lay representatives considered the evidence and agreed on answers to the following questions:

- Is the relationship between blood cholesterol levels and coronary heart disease causal?
- Will reduction of blood cholesterol levels help prevent coronary heart disease?
- Under what circumstances and at what level of blood cholesterol should dietary or drug treatment be started?
- Should an attempt be made to reduce the blood cholesterol levels of the general population?
- What research directions should be pursued on the relationship between blood cholesterol and coronary heart disease?

Panel's Conclusions

Elevated blood cholesterol level is a major cause of coronary artery disease. It has been established beyond a reasonable doubt that lowering definitely elevated blood cholesterol levels (specifically blood levels of low-density lipoprotein cholesterol) will reduce the risk of heart attacks due to coronary heart disease. This has been demonstrated most conclusively in men with elevated blood cholesterol levels, but much evidence justifies the conclusion that similar protection will be afforded in women with elevated levels. After careful review of genetic, experimental, epidemiologic, and clinical trial evidence, we recommend treatment of individuals with blood cholesterol levels above the 75th percentile (upper 25 percent of values). Further, we are persuaded that the blood cholesterol level of most Americans in undesirably high, in large part because of our high dietary intake of calories, saturated fat, and cholesterol. In countries with diets lower in these constituents, blood cholesterol levels are lower, and coronary heart disease is less common. There is no doubt that appropriate changes in our diet will reduce blood cholesterol levels. Epidemiologic data

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and over a dozen clinical trials allow us to predict with reasonable assurance that such a measure will afford significant protection against coronary heart disease.

For these reasons we recommend that:

- 1. Individuals with high-risk blood cholesterol levels (values above the 90th percentile) be treated intensively by dietary means under the guidance of a physician, dietitian, or other health professional; if response to diet is inadequate, appropriate drugs should be added to the treatment regimen. Guidelines for children are somewhat different, as discussed below.
- 2. Adults with moderate-risk blood cholesterol levels (values between the 75gh and 90th percentiles) be treated intensively by dietary means, especially if additional risk factors are present. Only a small proportion should require drug treatment.
- 3. All Americans (except children under 2 years of age) be advised to adopt a diet that reduces total dietary fat intake from the current level of about 40 percent of total calories to 30 percent of total calories, reduces saturated fat intake to less than 10 percent of total calories, increases polyunsaturated fat intake but to no more than 10 percent of total calories, and reduces daily cholesterol intake to 250 to 300 mg or less.
- 4. Intake of total calories be reduced, if necessary, to correct obesity and adjusted to maintain ideal body weight. A program of regular moderate-level exercise will be helpful in this connection.
- 5. In individuals with elevated blood cholesterol, special attention be given to the management of other risk factors (hypertension, cigarette smoking, diabetes, and physical inactivity).

These dietary recommendations are similar to those of the American Heart Association and the Inter-Society Commission for Heart Disease Resources.

- 6. New and expanded programs be planned and initiated soon to educate physicians, other health professionals, and the public to the significance of elevated blood cholesterol and the importance of treating it. We recommend that the National Heart, Lung, and Blood Institute provide the focus for development of plans for a National Cholesterol Education Program that would enlist participation by and contributions from all interested organizations at national, state, and local levels.
- 7. The food industry be encouraged to continue and intensify efforts to develop and market foods that will make it easier for individuals to adhere to the recommended diets and that school food services and restaurants serve meals consistent with these dietary recommendations.
- 8. Food labeling should include the specific source or sources of fat, total fat, saturated and polyunsaturated fat, and cholesterol content as well as other nutritional information. The public should be educated on how to use this information to achieve dietary aims.

- 9. All physicians be encouraged to include whenever possible a blood cholesterol measurement on every adult patient when that patient is first seen; to ensure reliability of data, we recommend steps to improve and standardize methods for cholesterol measurement in clinical laboratories.
- 10. Further research be encouraged to compare the effectiveness and safety of currently recommended diets with that of alternative diets; to study human behavior as it relates to food choices and adherence to diets; to develop more effective, better tolerated. safer, and more economical drugs for lowering blood cholesterol levels; to assess the effectiveness of medical and surgical treatment of high blood cholesterol levels in patients with established clinical coronary artery disease; to develop more precise and sensitive noninvasive artery imaging methods; to apply basic ceil and molecular biology to increase our understanding of lipoprotein metabolism (particularly the role of HDL as a protective factor) and artery wall metabolism as they relate to coronary heart disease.
- 11. Plans be developed that will permit assessment of the impact of the changes recommended here as implementation proceeds and provide the basis for changes when and where appropriate.

I. IS THE RELATIONSHIP BETWEEN BLOOD CHOLESTEROL LEVELS AND CORONARY HEART DISEASE CAUSAL?

The evidence supporting a causal relationship between blood cholesterol levels and coronary heart disease comes from a wealth of congruent results of genetic, experimental pathologic, epidemiologic, and intervention studies. These data establish beyond any reasonable doubt the close relationship between elevated blood cholesterol levels (as measured in serum or plama) and coronary heart disease. At the same time, it is equally clear that an elevated blood cholesterol level is not the only cause of coronary heart disease. Hypertension, cigarette smoking, diabetes mellitus, obesity, and physical inactivity along with a number of other risk factors such as age, sex, and family history are important contributing causes. There probably are other undiscovered contributing causes. However, we shall confine ourselves here primarily to a discussion of elevated blood cholesterol.

It is now firmly established that all cholesterol is carried in the blood stream in several protein-lipid combinations known as lipoproteins and that most of the blood cholesterol in humans is carried by specific low-density lipoproteins (LDL). Some is also present in high-density lipoproteins (HDL) and in very low-density lipoproteins (VLDL). The LDL particles, when present in excess in the blood, are deposited in the tissues and form a major part of a buildup in the artery wall to form atherosclerotic plaque. Atherosclerosis narrows the channels of the coronary arteries, the vessels that furnish the major blood supply to the heart muscle.

Genetic Evidence

Severe coronary heart disease can result from high blood cholesterol levels in the absence of any other contributing risk factors. This is clearly demonstrated by the accelerated and clinically catastrophic coronary heart disease in children with inherited hypercholesterolemia in its most severe form. These children lack the specific receptor that normally removes LDL from the blood, and as a result, they have very high LDL cholesterol levels from birth. They frequently suffer severe coronary heart disease, and death may occur even in childhood. Careful study of these diseased arteries reveals large quantities of cholesterol in the plaques.

The LDL receptor normally plays a critical role in regulating blood cholesterol levels in all mammals, including humans. It has been purified and fully characterized.

Studies suggest that a number of cases of clinically important coronary heart disease with less severe elevations of blood cholesterol may be explained by partial deficiencies of functioning LDL receptors, deficiencies induced by dietary and life-style factors. Thus, the high blood cholesterol in these patients has a similar basis to that in inherited hypercholesterolemia and, while less severe, probably has the same implications.

Experimental Pathology (Animal Model) Evidence

With improved use of the many existing animal models, a number of very important relationships between blood cholesterol, atherosclerosis, and coronary heart disease have been demonstrated:

- Many species (including several nonhuman primates) develop atherosclerosis when fed diets that raise their blood cholesterol levels.
- Studies over time demonstrate that hypercholesterolemic monkeys (and other species) develop intimal lesions that progress from fatty streaks to typical raised plaques to complicated ulcerated plaques resembling those seen in humans suffering from coronary heart disease.
- Hypercholesterolemia augments experimental atherosclerosis when arterial "injury" is present.
- Severe atherosclerosis in rhesus monkeys, usually a progressive process, regresses when the blood cholesterol is lowered substantially for an extended period by diet or by drugs.

Animal studies thus offer strong and persuasive evidence supporting the causal relatioship between blood cholesterol and atherosclerosis.

Epidemiologic Evidence

A large body of epidemiologic evidence supports the direct relationship between blood cholesterol levels and coronary heart disease:

• Comparisons among various populations throughout the world reveal a direct correlation between blood cholesterol levels and the occurrence of coronary heart disease; no population has been

- reported with a high rate of coronary heart disease and low blood cholesterol levels.
- People who have migrated to another country with a higher average blood cholesterol level gradually acquire the dietary habits, blood cholesterol concentration, and coronary heart disease rates of their new country of residence.
- Severity and frequency of raised plaques in the aorta and coronary arteries are strongly correlated with blood cholesterol levels.
- Populations experiencing severe dietary (especially fat) limitations and weight loss have been shown to have less atherosclerosis, coronary heart disease, and fewer heart attacks.
- Prospective studies such as the Framingham study have shown that elevated blood cholesterol levels in healthy people predict the future occurrence of coronary heart disease.
- Evidence emerging from multiple clinical trials, reviewed in the next section, clearly indicates that lowering blood cholesterol levels in patients with hypercholesterolemia decreases the likelihood of fatal and nonfatal coronary heart disease.

Thus, the evidence obatained from gentic, experimental, epidemiologic, and clinical intervention investigations overwhelmingly supports a causal relationship between blood cholesterol levels and coronary heart disease.

II. WILL REDUCTION OF CHOLESTEROL LEVELS HELP PREVENT CORONARY HEART DISEASE?

Our conclusion that reduction of blood cholesterol levels will reduce the rate of coronary heart disease is based partly on the evidence for cause-and-effect presented above and partly on the direct evidence from clinical trials noted below.

First, metabolic ward studies establish beyond reasonable doubt three dietary maneuvers that lower blood cholesterol levels: reducing the saturated fat content, increasing the polyunsaturated fat content, and reducing the cholesterol content. Second, a number of drugs have been developed that lower blood cholesterol levels. The issue of whether these interventions also influence coronary heart disease events has been more challenging.

In previous years, more than a dozen randomized trials of the effects of fat-controlled diets or drugs have been reported. Most showed some decrease in coronary heart disease event rates in the treated group, and the dietary trials carried out by Dayton et al. and by Leren et al. were particulary suggestive, producing 23 percent and 35 percent reductions in the incidence of coronary heart disease. However, no study considered individually could be regarded as conclusive: the sample sizes were too small, and there were in some cases unanticipated increases in non-cardiovascular deaths, although these were not statistically significant. An aggregate analysis of all unifactor blood-cholesterol-lowering trials, while not revealing an effect on total mortality, does indicate that

coronary heart disease rates can be reduced by reduction of blood cholesterol levels.

These findings have been extended by two recently reported randomized and blinded clinical trials of the efficacy of the cholesterol-lowering drug, cholestyramine. One of these studies, the Lipid Research Clinics Coronary Primary Prevention Trial, showed a statistically significant 19 percent reduction in the combined rate of fatal and nonfatal coronary heart disease in association with a 9 percent decrease in blood cholesterol level. The other study, the NHLBI Type II Coronary Intervention Study, showed a reduction in the angiographic progression of coronary artery disease. In addition, a third trial (the Coronary Drug Project) has recently presented information extending the earlier published finding that the use of nicotinic acid lowers the rate of recurrent coronary heart disease by demonstrating in long-term followup a decrease in overall mortality.

These findings, taken in conjunction with the results of the earlier studies, permit the conclusion that reduction of blood cholesterol level in people with relatively high initial levels will reduce the rate of coronary heart disease. The clinical trials are too limited to settle the issue of effects on overall mortality. However, the complete set of evidence, which includes information derived from animal, pathophysiological, metabolic and epidemiologic studies, makes it reasonable to presume that the reduction in coronary heart disease incidence will be accompanied by a reduction in overall mortality.

The magnitude of the reduction in coronary heart disease risk can be estimated from these clinical trials; they indicate that each 1 percent reduction in blood cholesterol level yields approximately a 2 percent reduction in coronary heart disease rates. This is remarkably similar to the magnitude of the beneficial outcome predicted from observational epidemiologic studies. Thus, for example, a 5 percent reduction in blood cholesterol level resultiong from the diets recommended below should reduce coronary heart disease rates by 10 percent. The absolute magnitude of this benefit should be greater in patients at high risk because of existing coronary heart disease or the presence of other risk factors such as cigarette smoking and hypertension. Reductions in disease rates of as much as 50 percent may be achievable in high-risk cholesterol patients who adhere well to a combination of effective drug treatment and a fat-controlled diet.

III. UNDER WHAT CIRCUMSTANCES AND AT WHAT LEVEL OF BLOOD CHOLESTEROL SHOULD DIETARY OR DRUG TREATMENT BE STARTED?

What Is Hypercholesterolemia?

A precise definition of hypercholesterolemia is difficult to establish. Often, an abnormally high level of a biologic substance is considered to be that level above which are found the upper 5 percent of the population (the 95th percentile). However, the use of this criterion in defining "normal" values for blood cholesterol levels in the

United States is unreasonable; coronary heart disease is our major cause of death and, in part at least, because a large fraction of our population probably has too high a blood cholesterol level. A review of available data suggests that levels above 200 and 230 mg/dl are associated with an increased risk of developing premature coronary heart disease. It is staggering to realize that this represents about 50 percent of the adult population of the United States. The consensus panel has chosen to define two levels of hypercholesterolemia, both of which are associated with an increased coronary heart disease risk, and both of which should be treated.

High-Risk Blood Cholesterol (Severe Hypercholesterolemia)

This category is defined as values at approximately the 90th percentile or above as determined by the Lipid Research Clinics Prevalence Study (see table for guidelines). It will include individuals with hereditary forms of high blood cholesterol and will require the most aggressive treatment. Withholding treatment subjects these individuals to unnecessary risk.

Moderate-Risk Blood Cholesterol (Moderate Hypercholesterolemia

This category is defined as values approximately between the 75th to 90th percentiles (see table for guidelines). It includes large numbers of people whose elevated blood cholesterol is due, in part, to their diet. The intensity of treatment is guided by the clinical and family history and the presence of other risk factors predisposing to coronary heart disease.

Values for Selecting Adults at Moderate and High Risk Requiring Treatment

(See special guidelines for management of children below.)

Age	Moderate Risk	High Risk
20-29	Greater than 200	Greater than 220
	mg/dl (5.17 mM)	mg/dl (5.69 mM)
30-39	Greater than 220 mg/dl (5.69 mM)	Greater than 240 mg/dl (6.21 mM)
40 and	Greater than 240	Greater than 260
over	mg/dl (6.21 mM)	mg/dl (6.72 mM)

How Should Adults With Hypercholesterolemia Be Treated?

The presence of high-risk and moderate-risk blood cholesterol should be confirmed by a repeat analysis. Although the initial sample may be obtained nonfasting, the repeat analysis should be obtained after an overnight fast so that a valid triglyceride level also can be determined.

After the secondary causes for hypercholesterolemia (e.g., hypothyroidism, nephrotic syndrome, dysproteinemias, diabetes mellitus, and obstructive liver disease) have been excluded, the primary cause should be evaluated. This includes family screening to detect the hereditary forms of elevated blood cholesterol and to

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identify other family members needing treatment. Measurement of HDL cholesterol is often helpful to determine if the elevated blood cholesterol is due to high levels of HDL (which is associated with a lower risk of coronary heart disease). In addition, a low HDL cholesterol (an independent risk factor) might guide a physician to be more aggressive in treatment of individuals with high or moderately high blood cholesterol.

Diet Therapy

The first step in the treatment of high-risk and moderate-risk blood cholesterol is diet therapy and caloric restriction for weight normalization in the overweight. Weight loss may reduce blood cholesterol, and a moderate level of physical exercise may be helpful in this regard. The dietary approach should be to lower total fat, saturated fat, and cholesterol consumption. The following guidelines are generally consistent with those of the American Heart Association and the Atherosclerosis Study Group of the Inter-Society Commission for Heart Disease Resources. We recommend a diet composed of approximately 30 percent of the caloric intake from fats and no more than 250 to 300 mg of cholesterol a day. An essential consideration is a reduction of the total saturated fat intake to 10 percent or less of total calories. It is recommended that polyunsaturated fat intake be increased but to no more than 10 percent of total calories. These changes can be readily made while maintaining intake of protein, vitamins, and minerals to satisfy the Recommended Dietary Allowance of the Food and Nutrition Board of the National Research Council.

Insufficient response to this diet may necessitate further restrictions of total fat to 20 to 25 percent of calories with saturated fat comprising 6 to 8 percent of the calories. The dietary cholesterol should be lowered to 150 to 200 mg/day (equivalent to American Heart Association Phases II and III diets).

The use of diet as a primary mode of therapy requires a major effort on the part of physicians, nutritionists, dietitians, and other health professionals. Lifestyle changes are difficult without adequate instruction, motivation, and encouragement. Education of physicians, as well as the general public, as to the value of reductions in dietary saturated fat and cholesterol will assit not only with treatment of patients with high- or moderate-risk blood cholesterol but also in achieving the goal of reducing the blood cholesterol levels of our entire adult population to less than 200 mg/dl (less than 180 mg/dl in those under age 30).

Drug Therapy

Drug therapy should be used only after a careful trial of diet modification using the most rigorous diet appropriate for the particular individual. Even when drugs seem appropriate, it is important to stress that maximal diet therapy should be continued. Several drugs, used singly or in combination, are now available. These include the bileacid sequestrants (cholestyramine and colestipol), nicotinic acid, probucol, and the fibric acids

(clofibrate and gemfibrozil). Of these, bile-acid sequestrants and nicotinic acid have been shown to reduce coronary heart disease. Clofibrate, while effective in treating one rare familial form of lipid abnormality (Type III hyperlipoproteinemia), is not recommended because it is not effective in most individuals with a high blood cholesterol level but normal triglyceride level. Moreover, an excess overall mortality was reported in the World Health Organization trial of this drug. We still do not have direct evidence for the safety of any cholesterol-lowering drugs when given over decades; therefore, drug treatment should be undertaken cautiously and its desirability should be periodically reevaluated, particularly in children.

Individuals with high-risk blood cholesterol (severe hypercholesterolemia), especially those with the hereditary form, may well require drug therpy in addition to dietary modification. Combined drug treatment (e.g., bile-acid sequestrant plus nicotinic acid) may be particularly effective. Several combined treatment regimens are under study. Individuals with moderate-risk blood cholesterol will usually respond adequately to diet alone. Judgment on the decision to use drugs in such patients must be made on a case-by-case basis, taking into account family history of coronary heart disease, existing coronary disease in the individual, coexistence of other risk factors, and age of the individual.

Who Should Be Treated?

As described above, individuals with high- and moderate-risk cholesterol levels (greater than the 75th percentile) should be treated with diet or diet and drugs. Furthermore, it is clearly recognized that it is a goal to encourage reduction of the blood cholesterol to approximately 180 mg/dl for adults under the age of 30 years and to approximately 200 mg/dl for individuals age 30 or older. This is recognized as a realistic "target" level that should be possible to achieve and that would be predicted to have a beneficial effect on coronary heart disease risk. As will be discussed in the following section, it is recommended that all individuals in the population consume a diet composed of approximately 30 percent of the calories as fat (10 percent or less saturated fat) and 250 to 300 mg of cholesterol a day in an attempt to shift the blood cholesterol levels in our population toward the lower levels observed in populations having much lower rates of coronary heart disease.

Both men and women at high risk, as defined above, should be treated similarly, even though premenopausal women have an apparent protection, and the onset of the disease occurs later than in men. However, as in men, the leading cause of death in women is coronary heart disease, and blood cholesterol is a risk factor. Despite the fact that direct intervention studies have not been conducted in women, there is no reason to propose a separate treatment schedule for women.

Studies are available that indicate a beneficial effect of treating high cholesterol levels in individuals with preexisting clinical disease (secondary intervention) as well as in individuals without preexisting clinical disease Lowering Blood Cholesterol to.. Bol. Asoc, Med. P. Rico - Julio 1985

(primary intervention). Because of their vulnerability, patients with established disease, including particularly patients with coronary bypass grafts, should be intensively treated. It is encouraging that the progression of established lesions may be retarded by appropriate dietary and drug therapy. The same may apply to the elderly patient. While there is no direct evidence on the benefit to be expected in the elderly, and while blood cholesterol becomes less important as a risk factor in old age, dietary treatment (with due attention to ensure nutritional adequacy) may still be helpful.

Special Guidelines for Management of Children

Identifying and treating children with elevated blood cholesterol levels is a subject for special consideration. It is desirable to begin prevention in childhood because patterns of lifestyle are developed in childhood. The moderate-fat and moderate cholesterol diets recommended for the population at large in this report should be suitable for all family members, including healthy children over the age of 2 years. For children, the diets should provide all nutrients in quatities adequate to assure growth and development and meet energy requirements. Excessive gain in weight should be avoided. The diet may be inappropriate in children or in the elderly if they are malnourished or have special nutritional requirements. For others, the diet plan is safe and nutritionally adquate.

Children at "high-risk" should be identified primarily be carefully obtained family histories rather than routine screening. The history should include parents, grandparents, and all first-degree relatives. A family history of hypercholesterolemia or premature coronary heart disease should alert the physician to obtain at least two blood cholesterol determinations. If the blood cholesterol level in such "high-risk" children is above the 75th percentile (approximately 170 mg/dl for ages 2 to 19 years), total and HDL cholesterol should be obtained. Those children with blood cholesterol levels between the 75th and 90th percentile (170 to 185 mg/dl) should be counseled regarding diet and other cardiovascular risk factors and then followed at 1-year intervals. Those with levels above the 90th percentile (over 185 mg/dl) require special dietary instruction and close supervision with evaluation of other risk factors. A child with a blood cholesterol level above the 95th percentile (greater than 200 mg/dl) on two occasions is in a special category and may have one of the hereditary hypercholesterolemias. Strict dietary intervention is indicated and will be sufficient for many children. Non-responders should be considered for treatment with a lipid-lowering agent, e.g., bile-acid sequestrant (such as cholestyramine). All family members should be screened.

Dietary management of children with elevated blood cholesterol levels should be part of total management that includes regular exercise programs, maintenance of ideal weight, avoidance of excess salt and avoidance of cigarette smoking.

What Screening Strategy Should Be Adopted for Finding Subjects With High Blood Cholesterol?

According to data from the National Center for Health Statistics, a high percentage of the American population sees a physician at least once every year. If a cholesterol level were determined on adults at these visits, many of the individuals with cholesterol levels above the 75th percentile would be identified in a relatively short time and should be evaluated and treated as described above. This physician- and clinic-oriented method for screening would be cost-effective. Obviously, some patients may not see a physician for several years, and it would be advisable to educate the public to the importance of knowing one's cholesterol level. In children, only a "family history screening" is recommended, that is, cholesterol levels should be obtained in those at higher risk because of a strong family history, as discussed above. Educational programs developed by voluntary and public health organizations in conjuction with the National Cholesterol Education Program of the National Heart, Lung, and Blood Institute, as recommended by this consensus panel, should alert all adults to the advisability of learning their cholesterol level.

While we are not at this time recommending mass screening, a feasibility study of various screening methods in adults should be considered. Screening necessitates the availability of laboratories capable of determining precisely and accurately the blood cholesterol and HDL cholesterol able to manage large numbers of new patients. Thus, prelimanary steps are needed before mass screening can be considered.

IV. SHOULD AN ATTEMPT BE MADE TO REDUCE THE BLOOD CHOLESTEROL OF THE GENERAL POPULATION?

Rationale for Recommendations to the General Population

Many compelling lines of evidence link blood cholesterol to coronary heart disease. There is also good evidence from epidemiologic studies that the relationship between level of cholesterol and level of risk for coronary heart disease covers virtually the entire cholesterol distribution for the U.S. population. In fact, recent epidemiologic studies suggest that the relationship holds even at the lower end of the spectrum of cholesterol levels found in our population.

The Japanese population, in comparison with the U.S. population, is characterized by a much lower average cholesterol level and a much lower frequency of coronary heart disease. The Finnish, on the other hand, have a much higher average cholesterol level and a much greater risk of coronary heart disease than do U.S. citizens. Furthermore, Japanese who have migrated to Hawaii and to San Francisco have higher cholesterol levels and a higher risk of coronary heart disease than nonmigrants. Compilation of all the available data suggests that it will be beneficial to lower the blood cholesterol of the average American.

In recent years, Americans have been changing their

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habitual diet in the direction we recommend, that is, by reducing their intake of total fat, saturated fat, and cholesterol and by increasing intake of polyunsaturated fat. This has been accompanied by a substantial reduction in the average blood cholesterol of the population. In addition, all-cause mortality, cardiovascular mortality, and coronary heart disease mortality have also decreased, but it is difficult to determine with certainty how much, if any, of this decrease is due to changes in diet, blood pressure, cigarette usage, or improved medical care. It is hoped that improved surveillance systems will clarify these issues.

Recommendations

In the general population, the basic intervention should be based on diet rather than drugs. We recommend a shift from the current typical American diet to one that is lower in total fat, saturated fat, and cholesterol. Diets will these characteristics are the usual diets consumed in a number of other countries, e.g., Japan and Greece. Life expectancy in these two countries is, at virtually every age, greater than that in the United States. This applies also to the life expectancy in middle age, when mortality from coronary heart disease begins to rise sharply.

The evidence justifies for men, women, and children ages 2 years and older the reduction of calories from fat from the present average level of 40 percent to 30 percent, calories from saturated fat to 10 percent or less, and dietary cholesterol no more than 250 to 300 mg daily. We recommend that calories from polyunsaturated fat be increased, but not exceed 10 percent of total calories. This diet is generally consistent with the most recent recommendations of the American Heart Association and the Atherosclerosis Study Group of the Inter-Society Commission on Heart Disease Resources. Equally important, individuals, health professionals, and health agencies must recognize the need to control obesity both to aid in controlling blood cholesterol levels and to reduce the other health risks of obesity. Other elements important to the prevention of cardiovascular disease, including avoidance of cigarettes, control of high blood pressure, and maintenance of reasonable levels of physical activity are recommended.

Means of Implementing Dietary Recommendations in the General Population

- If dietary intervention in the general population is to be effective, the eating habits of the entire family must be changed. Thus, the recommended diet should be available to all family members except those under age 2.
- Educational services that enable adults and children to make informed choices concerning their eating habits should be readily available, including ready availability of data on composition of natural and processed foods.
- Professional educational programs for physicians, dietitians, and other health professionals should be expanded to include adequate material on diet and heart disease.

• Specific food items consistent with the recommended diet should be available, accessible, and affordable.

- The food industry should accelerate its current efforts to develop, produce, and market leaner meats and other foods, including dairy products, with reduced total fat, saturated fat, and cholesterol content.
- Restaurants, including fast-food outlets, should make foods satisfying these diet recommendations available to their customers.
- Government and school food programs should serve meals consistent with these recommendations.
- Food labeling should include total calories, fat source and total fat, saturated fat, polyunsaturated fat, and cholesterol content as well as other essential nutritional information. If necessary, appropriate statutory or other changes to require such labeling should be seriously considered.
- A national cholesterol education program should be implemented for physicians, other health professionals (including those in training) and the public, its effectiveness should be periodically evaluated.

WHAT RESEARCH DIRECTIONS SHOULD BE PURSUED ON THE RELATIOSHIP BETWEEN CHOLESTEROL AND HEART DISEASE?

We know that blood cholesterol is causally related to coronary heart disease and that the atherosclerotic process can be influenced by intervention. However, much about lipid metabolism and about the mechanisms, of the atherosclerotic process remains unknown.

- Cellular and Molecular Biology—A better understanding of lipoprotein production and removal, lipoprotein receptors, and apolipoproteins is needed. More information is needed with regard to factors controlling the level of HDL and its role in preventing coronary heart disease. To learn whether diets very high in polyunsaturated fatty acids have any adverse effects, more information is needed regarding their biochemical and biological effects, including those of the highly unsaturated fatty acids found in fish oils. Research is also needed on the biology of vessel wall injury, on the cells that participate in atherosclerosis, and on the events that trigger thrombosis in atherosclerotic vessels.
- Clinical Investigation—Precisely defined diets and pharmacologic interventions to reduce blood cholesterol and other lipids must be studied in individuals under carefully controlled conditions. Research on the effectiveness of regimens to lower blood cholesterol and influence atherosclerosis, including surgical intervention, should also be conducted. Evaluation of these may involve atherosclerotic plaque measurement using safe, precise imaging techniques such as ultrasound, regional radioscintigraphy, magnetic resonance, and/or computer-enhanced radiography.
- Pharmacologic Research—New compounds that are more effective, economical, and safe for the reduction of blood cholesterol are needed. Development of

improved, more palatable, and less expensive bileacid sequestrants also is needed. Similarly, a search for pharmacologic agents that would favorably influence other elements of the atherosclerotic process is highly desirable.

- Food Product Research—The interface of human nutrition and human disease requires collaborative efforts within the agricultural, industrial, and health research communities. More food products that are high in nutritional quality and taste, yet low in fat and cholesterol, need to be developed.
- Research in Human Behavior—Study of how people choose their diets and how food habits can be improved are necessary. Studies designed to measure and enhance adherence to new nutritional behaviors and treatment programs are needed.
- Epidemiologic Investigation—The search for additional factors that initiate or affect the atherosclerotic process must be continued along with further studies of risk factors in major population subgroups, including blacks. As nutritional practices of the
- population change and as health professionals improve management of elevated blood cholesterol levels, ongoing monitoring of nutritional patterns, blood cholesterol levels, and disease and death outcomes is essential. An important corollary will be monitoring to assess disease incidence, prevalence, and case fatality rates. Research to assess the effects of blood cholesterol reduction on cardiovascular and all-cause mortality is needed. Overall safety of longterm intervention with diet and drugs should be investigated.
- Secondary Prevention—The effectiveness of lowering blood cholesterol by medical or surgical intervention to retard or reverse atherosclerotic lesions in arteries or bypass graffts of patients with established coronary heart disease requires further investigation.
- Community Applications—Community demonstration research to test the effectiveness of nutritioneducational programs that influence food choices and other risk factor behaviors of the healthy freeliving population is needed.



Fábrica de Tabaco de Mascar, en Sabana Grande, Puerto Rico.

El tabaco se trenza en sogas largas, que se venden por yardas. Los paquetes cilíndricos muestran como se prepara para exportarlo al extranjero. A las muchachas y mujeres que trabajan en las fábricas se les pagaba veinticinco centavos diarios, y a algunas aún menos.



DIAGNOSTICO ANGIOCARDIOGRAFICO



Rafael Villavicencio, M.D., F.A.C.C. Angel F. Espinosa-López, M.D.

Un joven de 13 años de edad con historial médico negativo para enfermedad cardíaca y asintomático es referido a nuestra institución para estudios diagnósticos invasivos.

Al examen físico se aprecia un adolescente bien desarrollado y nutrido con una frecuencia cardíaca de 70/min., sonidos cardíacos buenos y un "precordio tranquilo". No hay accesibilidad ventricular y el PMI se palpa en el 5° espacio intercostal izquierdo 1 cm. lateral a la línea medio clavicular. Se aprecia un soplo sistólico-eyectivo, rudo, grado 2/6 en el precordio superior con irradiación a lo largo del reborde esternal izquierdo y la espalda. El S_1 es normal y el S_2 se desdobla bien, con un componente pulmonar (P_2) también normal. No hay arrastre diastólico, "clicks" ni frote pericárdiaco. No se palpa visceromegalia. La pulsación arterial es fuerte en la región antecubital pero está disminuida en la región femoral. La presión arterial en el brazo fue de 150/80, y en la pierna del mismo lado la presión sistólica fue de 90 mm Hg usando el método de "flush".

El electrocardiograma (ECG) demostraba hipertrofia ventricular izquierda discreta con fuerzas ventriculares izquierdas posteriores prominentes. (S profunda V₄R-V₂) La radiografía de tórax solo demostró cardiomegalia y una vascularidad pulmonar normal.

En el laboratorio cardiovascular se le hizo un ventriculograma retrógrado, parte del cual se ilustra en la figura 1 y que provee el diagnóstico.



Ventriculograma izquierdo (vista lateral) por via retrógrada donde puede apreciarse el arco aórtico. LV-ventrículo izquierdo, MVR-anillo mitral, AoV-Válvula aórtica, AA-aorta ascendente, CC-circulación colateral, DA-aorta descendente

¿CUAL ES SU DIAGNOSTICO?

Hospital Pediátrico Universitario, Departamento de Pediatría, Sección de Cardiología Pediátrica, Recinto de Ciencias Médicas, Universidad de Puerto Rico.

Coartación de la Aorta

La coartación de la aorta (COA) es una constricción de la aorta (ya bien sea un segmento corto o largo) que está casi invariablemente localizada en la unión del ducto arterioso y el arco aórtico, inmediatamente distal a la arteria subclavia izquierda. En los pacientes con COA es de suma importancia determinar si el suplido principal de sangre de la parte baja del cuerpo es proveniente del ventrículo izquierdo via la aorta ascendente, tipo adulto (figura 2) o del ventrículo derecho através de la arteria pulmonar, ducto arterioso patente y aorta descendente (tipo infantil), figura 3. Es también de gran importancia en la COA el determinar la presencia de cardiopátias asociadas, pues la incidencia de defectos asociados es alta; siendo las más frecuentes: el ducto arterioso patente (PDA), la comunicación interventricular (VSD), la estenosis aórtica, y anomalías de la válvula mitral. La válvula aórtica bicúspide es la más frecuente de todas estas anomalías asociadas a la COA, ocurriendo en aproximadamente 85% de los casos.^{1, 2} La COA es a su vez la cardiopatía más frecuente en el síndrome de Turner.

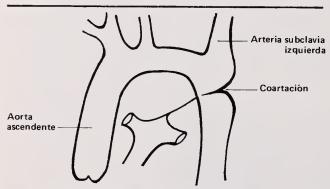


Figura 2. Coartación de la aorta del "tipo adulto" o segmento corto.

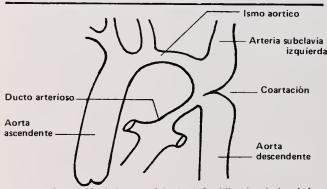


Figura 3. Coartación de la aorta del "tipo infantil" o hipoplasia tubular.

La COA es una malformación frecuente, en su forma aislada constituye la quinta cardiopatía congénita en orden de frecuencia.³ En infantes es la cuarta cardiopatía congénita más frecuente según se informó en un estudio reciente,⁴ representando el 7.5% de todos los infantes menores de un año con cardiopatías congénitas. La COA aislada es más frecuente en varones en una proporción de 1.7 a 1, mientras que en la infancia la predominancia masculina es menor.

La COA que se diagnostica después de la infancia rara vez poduce síntomas. En el examen físico es característico los pulsos fermorales disminuidos o ausentes y el diferencial de presión arterial entre las extremidades superiores y las inferiores. La mayoría de las veces hay hipertensión arterial en uno o ambos brazos. Este diferencial en presiones se considera un hallazgo patógnomónico de COA. Un soplo sistólico está presente en cerca de 90% de los casos. Es por lo regular corto, de tonalidad ruda y se oye mejor en el reborde esternal izquierdo y la espalda. Este soplo puede originarse de la propia coartación, de la circulación colateral y/o una válvula aórtica bicúspide. Cuando hay una circulación colateral bien desarrollada pueden apreciase soplos continuos a los lados y región posterior del tórax.

El ECG en la coartación aislada puede ser normal o demostrar hipertrofia ventricular izquierda. Radiográficamente el tamaño del corazón puede ser normal o demostrar cardiomegalia con configuración izquierda. Las muescas costales ("rib notching") son raras antes de los 6 años de edad. Este hallazgo radiográfico se explica por la erosión que causan los vasos colaterales dilatados en el borde inferior de las costillas.⁵

Si se logra pasar através del área de la coartación el aortograma retrógrado provee el diagnóstico y puede precisarse el lugar y magnitud de la coartación (flecha en figura 1). Debido al gran avance obtenido con la ultrasonografía el estudio angiográfico para la COA puede obviarse en algunas ocasiones.

El pronóstico de los niños con COA depende de las características anatómicas del defecto, su diagnóstico temprano y la técnica quirúrgica a utilizarse. Se ha logrado la reparación exitosa de este defecto con cardiopatías asociadas en las primeras semanas de vida, sin embargo en la mayoría de los casos la reparación quirúrgica de la COA aislada se lleva a cabo luego del primer año. Antes de esta época las posibilidades de recoartación son mayores.

Al presente se recomienda que la reparación quirúrgica electiva de la COA (tipo adulto) se realize entre los 2 y los 4 años, o más temprano cuando hay hipertensión severá y signos de insuficiencia cardíaca o cardiomegalia. Siguiendo este enfoque terapéutico es posible evitar las complicaciones cardiovasculares en la adolescencia. Aún en los casos raros de recoartación en que se requiere una segunda intervención quirúrgica, esto se considera preferible a una hipertensión arterial de larga duración, hipertrofia ventricular izquierda crónica y la eventual disfunción miocárdica que le sigue en aquellas ocasiones donde el tratamiento quirúrgico se lleva a cabo más tarde.

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ASOCIACION PUERTORRIQUEÑA DEL CORAZON

SESION CIENTIFICA ANUAL CARDIÓ 85

13, 14, 15 DE SEPTIEMBRE DE 1985 CERROMAR, DORADO RESUMEN DE PONENCIAS (CALL FOR ABSTRACTS)

El Comité del Programa Científico invita a enviar abstractos de trabajos originales para considerarse para presentación durante la sesión científica que se efectuará los días 13, 14, 15 de septiembre de 1985, como parte de la Asamblea Anual de la Asociación Puertorriqueña del Corazón.

Para más información escriba a:

Dr. Salomón Monserrate Presidente, Comité Científico Asociación Puertorriqueña del Corazón Calle Cabo Alverio #554 Hato Rey, Puerto Rico 00918



ECHOCARDIOGRAPHY CASES

Charles D. Johnson, M.D., F.A.C.C.

Doppler, M-mode and Two-Dimensional Echocardiography In Ventricular Septal Defect

Charles D. Johnson, M.D., F.A.C.C.

Ventricular septal defect (VSD) is a common congenital heart defect. Echocardiography and Doppler echocardiography have assumed extremely important and critical roles in the diagnosis and follow-up of this lesion, as illustrated by the following case and review.

This 15-day-old baby had a muscular VSD detected by direct two-dimensional echocardiography. Studies were performed with a Honeywell echocardiograph machine (Biosound. Indianapolis, Ind.)



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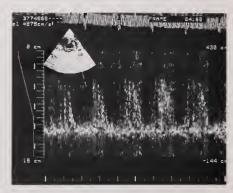


Figure 1. A two-dimensional echocardiographic freeze-frame view from the parasternal shortaxis position at the level of the papillary muscles of the left ventricle (LV). Time markers are present at the top and bottom margins (1 second, S, between the heavy lines). An A-mode trace with ramp and gain, and a depth scale in cm are located on the left side, and an electrocardiogram at the top.

Echo drop-out is present at the anterior portion of the interventricular septum (VS) exiting into the right ventricle (RV), compatible with an anterior muscular VSD.

Figure 2. Two-dimensional echocardiogram. Parasternal long-axis view. The VS is discontinuous in its muscular midportion. The VS and LV posterior wall may be hypertrophied, and the left atrium (LA) enlarged (very unusual at 15 days of age).

Figure 3. Doppler echocardiogram. Pulsedwave Doppler (PWD), using high pulse repetition frequency. Parasternal short-axis view. A depth scale is located on the left side of the freeze-frame and a velocity scale on the right margin (10 cm/S for each step-level). The SV was placed on the right, anterior side of the VS at the VSD. There is systolic positive flow toward the transducer, manifesting jet velocity. The peak flow velocity of the defect was 2.78 m/S. The calculated pulmonary-to-systemic flow ratio, Op/Os, was 4:1, denoting a large shunt. The calculated Timeto-Peak velocities (TPV) were borderline at 90, 100 and 110 mS. Also, mean transatrial septal velocity was 37 cm/S, compatible with an additional atrial septal defect (ASD).

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Discussion

M-mode echocardiography of a VSD may reveal:

- 1. A normal study if the left-to-right shunt is small.
- 2. A dilated LA and LV (LV volume overload) in infants with a large left-to-right shunt; LV end-diastolic volume and mass related to the Qp/Qs-indirect indices. The RV body, aortic (Ao) root and septum are typically normal. The LV wall and VS may be thickened. Echo dimensions may be increased in proportion to the elevation of Qp/Qs; if the LA/Ao ratio is >1.4:1, the Qp/Qs may be > 2:1. If the Qp/Qs is >2:1, then the LA/Ao ratio may equal 1.4 or greater. The Z and Y axes should be mesured.
- 3. Exaggerated VS and LV posterior wall motion may possibly be present; LV shortening fraction may be increased. The VS may be displaced anteriorly.
- 4. There may be discontinuity of echoes between the superior VS and anterior wall of the Ao if the defect is large; but this is insensitive with false negatives and false positives (artefactual dropout, transducer placed closer to the great vessels or directed medially, rotation of VS during the cardiac cycle; too rapid scan from the Ao to the mitral valve; false overriding of the Ao occurs). Scanning between the LV apex and Ao should be carried-out
- 5. Fuzzy fluttering, systolic echoes of the tricuspid valve (poor).
- 6. Fluttering and augmented excursion of the mitral valve (poor).

- 7. VSD plus Ao regurgitation- Ao root dilatation, diastolic fluttering of anterior leaflet of mitral valve and LV volume overload.
- 8. Pulmonic valve fluttering vibration. Dilated right pumonary artery (PA)
- 10. With marked pulmonary hypertension (PH), there may be a large RV body but normal LA, LV and Ao.

Two-Dimensional

Views comprise: Parasternal long-axis view- for diagnosis of malalignment and some perimembranous defects; Short-axis. Apical 4-chamber with variable angling - malalignment and perimembranous. Subcostal 4-chamber-detects all defects, and short-axis - perimembranous, malalignment, AV canal, subpulmonic, and perhaps muscular defects. False positive drop-out does not occur.

Right sternal border with transducer angled medially toward the tricuspid valve; partial right lateral decubitus position.

Multiple views and planes should be utilized, using high frequency 3.5, 5 and 7.5 MHz transducers.

There may be:

- 1. direct visualization of the defect may reveal lack of, fall-out or discontinuity of VS echoes.
- 2. T artifact bright echoes from margins of the defect in shape of the letter T; edge of the defect elongating the echo from beam-width artifact; broadening of septal edges around the defect.
- 3. Defects as small as 2-4 mm can be detected, depending on the location, the transducer, instrument and persistence of search. The size varies from view to view and during different phases of the cardiac cycle; it may be larger at end-diastole.
- Color-coded methods have been applied for visualization of VSDs.

Anatomical Types

- 1. Perimembranous or membranous subaortic defects the subcostal view questionably offers the highest specificity; the apical 4-chamber view is applicable but is associated with false positive drop-out. Parasteranal and subcostal long-axis views. These defects are confluent with the Ao root, but are obscured by the tricuspid valve in diastole; they may be multiple.
- 2. Supracristal (subpulmonary, doubly-committed sub-aortic). Use subcostal long and short-axis, apical 4-chamber, parasternal long and short, and RV outflow tract (RVOT) views. The defect is immediately below the pulmonic valve without septal muscle between the defect and the valve, but a clear space between the VS and Ao root, a virtual absence of the infundibular septum sometimes allows both semilunar valves to lie adjacent to the defect. The defect is frequently associated with prolapsing of the right anterior Ao valve leaflet through the defect into the RVOT producing anomalous linear echoes. Coarse vibrations in echogram of the pulmonic valve.

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- 3. Muscular defects (posterior, mid, apical, anterior, subaortic). May be multiple. All views may be used including the RVOT view for outlet defects. An apical defect is located at the junction of the VS and LV free wall. Low defects may be difficult for both imaging and for Doppler, with high false negative and false positive (large RV trabeculations) rates and difficulty with SV threading due to their small size and circuitous course.
- 4. Malalignment (large subaortic), such as tetralogy of Fallot, truncus arteriosus, Double Outlet RV (anterior), Transposition of the great arteries with subvalvular pulmonic stenosis (posterior). All views. The malaligned septal crest lacks continuity to the Ao, which overrides; the infundibular septum is displaced anteriorly or posteriorly.
- 5. Doubly-committed subarterial defect Parasternal short-axis, and subcostal views. The defect extends up to below the pulmonic valve, without infundibular septum beneath the right coronary cusp. A subaortic defect is beneath the right coronary cusp and extends to the tricuspid ring.
- LV-to-RA Tunnel Coarse systolic fluttering and distortion of septal tricuspid valve leaflet. Acquired direct two-dimensional visualization from parasternal view.
- 7. VSD of AV canal, Neufeld type; Inlet Posterior. Apical 4-chamber views (future communication).
- 8. VS Aneurysm of a closing membranous defect. M-mode, two-dimensional techniques, realiable. Parasternal long-axis and apical 4-chamber view with cranial and anterior angulation; subcostal. Typical findings are the appearance of a windsock pouch, aneurysmal sac or curvilinear sickle, dome-shaped image along the right side of the side of the VS jutting or bulging toward the RV during systole. Systolic fluttering and anterior motion of the tricuspid valve has been observed. Tricuspid valve tissue adjacent to the septal defect and a tricuspid pouch must be excluded.
- 9. VSD with prolapsed Ao valve. High frequency diastolic fluttering and nonparallel motion of Ao valve; abnormal echoes in the LV cavity; an infracristal defect may result in prolapse of the noncoronary cusp into the RVOT and fine diastolic flutter.
- 10. A postoperative VSD. Use parasternal long-axis views of the LV and RVOT. The teflon patch may produce a strong, linear echo. A blood leak may show a large echo interruption at the margin of the defect. The ability exists to assess LV function, abnormal VS motion, LA/Ao ratio, end-diastolic volume and mass. Reliable.
- 11. Myocardial infarction vs Rupture. The clinical diffentiation from papillary muscle rupture is inexact. Two-dimensional and Doppler echocardiography are useful in the Coronary Care Unit. Short-axis and apical 4-chamber views. There may be: RV dilatation, septal akinesis or dyskinesis, decreased mitral valve diastolic slope, a suggestion of increased mitral valve flow, increased tricuspid valve excursion, and discontinous echoes with communication between

the LV and RV or septal rent. An aneurysmal bulging of the LV may exist without seeing the defect. Systolic thinning and akinesis of the apical VS was observed on an apical 4-chamber view. Turbulence along the right side of VS and abnormal flail motion of the upper VS have been noted. However, because it may be small or consist of a linear tear, it may not be directly visualized by two-dimensional echocardiography. Positive LV contrast with or without RV contrast is more sensitive for diagnosis and localization than direct visualization, and it is rapid and safe. Yet, it may be difficult to find a positive contrast echoin the LV (diastole) and a thin negative jet in the RV.

- 12. Traumatic VSD. Seen directly with two-dimensional imaging and contrast.
- 13. VSD with Coarctation of Ao-Subcostal and precordial views were used. Overriding of the Ao and LV outflow tract narrowing; the infundibular septum may be displaced posteriorly into the outflow tract. Various types of VSDs and morphology were encountered.
- 14. For membranous, malalignment and posterior defects the sensitivity of two-dimensional echocardiography is 74-94%, and the specificity is 88-91% (67% for subpulmonary and 37% for muscular defects); accuracy is 89-98% if the patient's age is under one year. The pulmonic valve preejection period/RV ejection time ratio is insufficiently accurate in the individual patient.
 - In a large study, two-dimensional echo was found reliable for diagnosing subaortic, inlet, small, medium and large subtricuspid and most large central and apical muscular defects. There were mistakes as: a second muscular defect or small apical or outlet defect, subpulmonary defect and distinction of doubly-committed subarterial from subaortic VSDs. Two-dimensional echocardiography was believed capable of replacing invasive investigations in the uncomplicated VSD before surgery.
- 15. Contrast Studies. Peripheral injection of contract in a right arm vein.
 - A. Left-to-right shunt Negative contrast effect on right side of VS superimosed on contrast-filled RV, usually diastolic; detectable in presence of a small bidirectional shunt; there may be a small right-to-left shunt as well in early diastole in patients with RV pressure approaching two-thirds of the LV pressure. But, not as sensitive, in general, near 60-80%, and the method cannot detect small VSDs. LA or LV catheter injection of contrast.
 - B. Right-to-left shunts, Eisenmenger's syndrome when RV systolic pressure is 50% of systemic pressure, or reaches or exceeds 70 mm Hg. The contrast moves from the RA to RV, to the LV above the mitral valve in the LV outflow tract. Right-sided contrast studies show different patterns depending upon the RV and LV pressures.

Contrast studies can identify communications that are too small to image even with high resolution real-time scanning.

Doppler Echocardiography

Continuous wave Doppler (CWD) and then PWD, plus two-dimensional echocardiography as guidance, or Doppler without imaging. Left parasternal, lower parasternal, or subcostal transducer locations; site of the thrill. Search for high frequencies, which can be recorded with PWD and a filter with highest cut-off frequencies, a lower frequency transducer, lower gain and spectral analysis. Doppler enables localization of the defect(s). Systolic study reveals pronounced chaotic, turbulent, rough harsh flow of multiple broad spectral echoes on the right side (or low pressure side) of the VS, in the maximal RV jet, with high velocity toward the transducer. There are high frequencies and many low frequencies of high intensities. These may be traced with the SV into (harsh, turbulent systolic) and through the VS into the LV where smooth laminar systolic flow is found. Normally, RV and LV flows are smooth and there is no flow in the VS. Holosystolic high velocity turbulence may be encountered by mapping along the right side of the VS and into the RVOT and PA, as well as in the RV body but to a lesser extent in the RV apex (muscular defects). Diastolic RV flow may be smooth. The Series Effect (extention of the flow disturbance downstream) and the Vortex Shed Distance may displace the origin of the flow disturbance into the RVOT, main and right PAs. The PA velocities in VSD are augmented (such as mean 33, peak 110 cm/S; normal mean 20 and peak 78 cm/S, and the ± 6 dB spectral width 30 cm/S. High pulse rate frequency or CWD may be necessary to obtain the peak velocity. PH and right-to-left shunting may alter the characteristic RV flow pattern, and it may not be possible to follow flow through the VS without imaging. There is less turbulence which is located in the LV outflow tract at the Ao valve. If RV and LV pressures are equal, there may be no flow signal; flows recorded toward the PA. Early systolic flow only corresponds to an early short systolic murmur of a small defect, and diastolic flow may detect a silent, highvelocity VSD. Early and late strong low-velocity signals reflect diastolic flow through the defect; in many patients if the velocity is higher it indicates elevated LV diastolic pressure. The breadth and degree of a VSD jet may or may not be a clue to VSD size; some of the smallest are very turbulent and difficult to track, while some larger defects have mild turbulence covering a broad area. Mitral valve velocities and pressure drop are augmented, but pressure half-time is normal.

A residual VSD with aneurysm formation can be recorded by Doppler. In a LV-RA Tunnel, there may be systolic negative turbulence when the SV is positioned near the defect.

Doppler and M-mode echocardiography, but even superior PWD and two-dimensional echo (2.4 MHz and 4-6 KHz pulse repetition frequency) have proven useful for the early diagnosis of myocardial infarction-induced VS rupture, site and size in the Coronary Care Unit. The SV is placed parallel to flow. The apical 4-chamber view delinates the VS well, and demonstrates left-to-right high velocity positive or negative flow through the VS during systole and diastole as uni-or bidirectional turbulent flow, with aliasing (but the flow velocity may be low), and

right-to-left slow diastolic flow into the LV, with presystolic augmentation, away from the apical transducer. Doppler may reveal VS rupture even if no discontinuity or tear is evident on two-dimensional imaging. Direct quantitation of flow over the VSD was not possible due to aliasing of the high velocity and lack of knowledge of the area of rupture, but Qp/Qs ratio can be estimated from Ao and PA flows.

For determination of pumonary-to-systemic flow ratio (subcostal, precordial short-axis views), Qp/Qs, PA flow or RVOT flow (if PA flow is too disturbed to determine the velocity) or the mitral valve orifice method of flow may provide pulmonary flow, while Ao flow can provide Qs. Limitations comprise: RVOT stenosis with its turbulence, high velocity, aliasing and spectral broadening; semilunar valve regurgitation which causes overestimation of flow; and patent ductus arteriosus (PDA), which induces an underestimation of Qp/Qs since it connects distally to the sampling site. Color-coded Doppler flow mapping is in the early stages of experience.

RV systolic pressure may be estimated. Left sternal border and apex. CWD and PWD. 2 MHz transducer. From the systolic arm blood pressure, the pressure difference or drop between the LV and RV across the VSD derived from: $P_1 - P_2 = 4V^2$ (P_1 , $P_2 = LV$ and RV systolic pressures; V = peak velocity). A normal RV systolic pressure without PH is characterized by a high velocity high frequency and a high pressure drop (normal blood pressure); elevated RV pressure produces a decreased velocity across the defect and an increased velocity of the associated tricuspid regurgitation (TR).

PA pressure may be estimated by: a Pc-To interval and heart rate. (RV Isovolumic Relaxation Time). b. RPEP/RVE 0.35.

Pc - pulmonic valve closure; To - tricuspid valve opening. Audio signals-

Doppler techniques may able to detect multilevel shunts, even if silent. If PA flow is rough in systole and normal in diastole, an additional PDA is not likely. If there is a VSD with a small or normal LA and no PDA, any associated ASD may be small. A tetralogy of Fallot may be diagnosed; the signals are only minimally disturbed in Truncus Arteriosus.

The Doppler echocardiographic technique with M-mode or two-dimensional echocardiography possesses a sensitivity of 90% and specificity of 98% in VSDs (less in some defects), depending on the position of the defect, PA pressure and resistance, and the direction of flow across the defect. It can detect a VSD too small to be easily on two-dimensional echocardiograms. It, thus, offers the unique ability to detect and localize abnormal flow patterns.

Differential Diagnosis

- 1. Spurious, factitious septal drop-out, due to excessive medial angulation of the transducer and decreased echo reflection from the VS, etc.
- Muscular VSD must be distinguished from intertrabecular spaces. Multiple VSDs can be detected or

missed, and postoperative residual shunts detected. Following repair of ostium primum ASD and cleft mitral valve, there may be a diastolic flow velocity signal recordable into the RV similar to diastolic shunting in VSD. AV canal and inlet defects may present problems.

- 3. Acquired VSD as after myocardial infarction (versus No. 4)
- 4. Mitral regurgitation (MR)- a turbulent systolic flow is recordable from the LA.
- 5. PDA. Coronary artery fistula to RV; sinus of Valsalva aneurysm rupture to RV (high diastolic velocities). Subaortic stenosis. Semilunar valve regurgitations.
- 6. Subpulmonic VSD from RVOT obstruction. Pulmonic and subpulmonic stenosis systolic turbulence confined to RVOT, or into the PA, flow away from transducer and a localized increase in velocity. CWD facilitates. An aneurysm of the muscular or membranous VS must be differentiated from RVOT muscular obstruction.
- 7. TR, which is common in VSDs. Both VSD and TR have similar systolic durations, but the flow signal of TR is obtained with a different beam angle and is away from the transducer, rather than toward, and it has a different velocity. This must be distinguished from a LV-RA shunt. VSD may occur with an ASD.

Acknowledgement

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ASOCIACION PUERTORRIQUEÑA DEL PULMON

CAMPAMENTO DE VERANO PARA LA EDUCACION Y REHABILITACION DEL NIÑO ASMATICO (V.E.R.N.A.)

Objetivo:

Los Campamentos V.E.R.N.A. tienen como objetivo el educar y promover la rehabilitación de niños que padecen de asma bronquial en Puerto Rico. Para lograr dicho objetivo lleva a cabo actividades educativas, deportivas, recreativas y culturales que ayuden a mejorar la condición física y emocional del niño.

V.E.R.N.A. ¿Para quién?

Los campamentos van dirigidos hacia aquellos niños de ambos sexos con asma que por su severidad limitan significativamente su asistencia a la escuela y su participación en actividades de su edad. Incluye además aquellos niños que requieren visitas frecuentes a Sala de Emergencia o que por su condición se ve afectada la relación del niño con la familia misma. En V.E.R.N.A. se ofrecen los servicios de enfermería todo el tiempo.

Un grupo de médicos especialistas evaluarán diariamente a los niños participantes que así lo requieran.

Cuenta además con un director de deportes dinámico y personal especializado para el desarrollo de las actividades.

Requisitos:

- Niños que padezcan de 6 o más episodios asmáticos al año, que requieran medicamentos diarios o vacunación semanal para estar libre de síntomas.
- 2- Niños de ambos sexos entre las edades de 8-12 años (no haber cumplido los 13).
- Complementar la forma de solicitud en o antes de la fecha límite.
- 4- La participación de por lo menos uno de los padres o encargados en una actividad educativa y de orientación.

Dale la oportunidad a tu niño de vivir unas experiencias inolvidables que no sólo le servirán para recrearse sino para mejorar su salud física y mental. Para mayor información, comunícate con la Asociación Puertorriqueña del Pulmón más cercana:



San Juan 765-5664

Ponce 840-2585

What can you do for hypertensives like Don S?



Rely on one-tablet-a-day dosage and cardioselectivity.*

"Real life" efficacy

Don S represents 899 black patients between 56 and 70 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even in Don S's racial and age group.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Compatible with cimetidine and ranitidine

TENORMIN is not metabolized by the liver. Its pharmacokinetics are unaffected when administered concomitantly with cimetidine or ranitidine. This compatibility of TENORMIN with today's widely prescribed $\rm H_2$ receptor antagonists makes it a logical choice for hypertensives like Don S who are under treatment for a coexistent ulcer.

*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁶ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



For Don S...and virtually all your hypertensive patients

TENORMIN® (atendal)







TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN* (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2"-hydroxy-3"-(1-methylethyl) amino] propoxy]-. Atenolol (tree base) has a molecular weight of 266 ft its a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37° C and a log partition coefficient (octanol/water) of 0.23. It is treely soluble in 1N HCI (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C). INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a third dependence.

triaduce-type dicients.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overticardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further

function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics. TENORMIN should be administered cautiously. Both digitalis and atenoloi slow AV conduction. In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac latilure, patients should be fully digitalized and for be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic. TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial inflarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overl angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated it withdrawal symptoms occur. drawal symptoms occur

drawal symptoms occur
Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN
GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do
not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is
not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated
at 50 mg and a beta;-stimulating agent (bronchodilator) made available. It dosage must be
increased, dividing the dose should be considered in order to achieve lower peak blood

levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN betore surgery in this case, 48 hours should be allowed to elapse between the last dose and anesthesia. It treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients it a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxinosis from whom TENORMIN herapy is to be withdrawn should be monitored closely.

should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impared renal function (see DOSAGE AND ADMINISTRATION)

Drug Interactions: Catecholamine-depleting drugs (eg. reserpine) may have an additive effect when given with beta-blocking agents Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg \times kg / day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding

Fertility of male or temale rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times

the maximum recommended human dose) was unaffected by atenoiol administration

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuo-

lation of epithelial cells of Brunner's glands in the duodenum of both male and temale dogs at all tested dose levels of atenolof (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol·kg/day (150 and 75 times the maximum recommended human dose,

respectively)

USAGE IN PREGNANCY: Pregnancy Category C. Alenolol has been shown to produce a doserelated increase in embryo / letal resorptions in rats at doses equal to or greater than 50 mg / kg or
25 or more times the maximum recommended human dose. Although similar effects were not seen
in rabbits, the compound was not evaluated in rabbits at doses above 25 mg / kg or 12.5 times the
maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justities the
potential risk to the faits. potential risk to the fetus

Potential has to the letus Mursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving. atenolol

atenolol Pediatric Use: Safety and effectiveness in children have not been established ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg., by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where trequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages. Iirst trom the U.S. studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects) and the first studies (volunteered side effects) are studies (volunteered side effects). eered and elicited side effect

teered and elicited side effects)

U.S. STUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)
GASTROINTESTINAL. diarrhea (2%-0%), nausea (4%-1%)
RESPIRATORY (See WARNINGS) wheeziness (0%-0%), dyspnea (0.6%-1%)

RESPIRATORY (See WARNINGS) wheeziness (0%-0%), dyspnea (0.6%-1%) TOTALS U.S. AND FOREIGN STUDIES: CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%), CENTRAL NERYOUS SYSTEM: NEUROMUSCULAR dizziness (13%-6%), verigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%) (ASTROINTESTINAL diarrhea (3%-2%), nausea (3%-1%) RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%) MISCELLANEOUS There have been reports of skin rashes and /or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered it any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: in addition, a variety of adverse effects have been reported.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenoiol).

TENCHMIN (atenoio).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catalonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased per-

place, soft-terminentory loss, entolional admity with slightly clouded sensorium, decreased per-formance on neuropsychometrics

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alope reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension.

dosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension bronchospasm, and hypoglycemia in the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted Bradycardia: Atropine or another anticholinergic drug Heart Block (Second or Third Degree): isoproterenol or transvenous cardiac pacemaker Congestive Heart Failure: Conventional therapy: Epinephrine rather than isoproterenol or nor-appearance may be useful in addition to stronger and digitals.

epinephrine may be useful in addition to atropine and digitalis Bronchospasm: Aminophylline, isoproterenol, or atropine.

Bronchospasm: Armnophylline, isoproterenol, or atropine. Hypoglycemia: Intravenous glucose. DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to duretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit. TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min 1.73 m² (normal range is 100-150 ml/min /1.73 m²); therefore, the tollowing maximum dosages are recommended for patients with renal impairment.

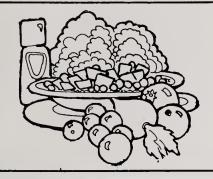
Creatinine Clearance (ml. min · 1 73 m²)	Atenolol Elimination Halt-lite (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg affer each dialysis, this should be done under

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked talls in blood pressure can occur HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolot) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolot): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets. Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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MEDICAL ASPECTS OF NUTRITION

Enteral and Parenteral Nutrition of Low Birth Weight Infants*

John W. Reynolds, M.D.**

In the last decade, the survival of low birth weight (LBW) infants has greatly increased as a result of improvements in techniques of and availability of high risk perinatal care. LBW infants are those under 2500 gm birth weight and include those who are premature (less than 37 week gestational age) and those small because of intrauterine growth retardation. Over 90% of LBW infants over 28 weeks gestation and 40%-50% of those of 26 weeks gestation now survive. Thus, there is an increasing challenge to provide the enteral (oral) nutrition needed by these very small infants for not only steady growth in lenght and weight, but also appropriate maturation and development of their immature organ systems. Parenteral (intravenous) nutrition also is important in the care of these infants. Their initial multiple organ system adaptation problems dictate the need frequently to delay the onset of enteral feedings and then to increase the volume slowly. Thus, parenteral nutrition is needed as a supplement during the period of slow adaptation of the infant's intestinal tract to enteral feedings. Parenteral nutrition is needed particularly in infants under 1500 gm birth weight, but may be indicated in any infant facing a delay in reaching full oral feedings for whatever reason.

The standards for adequate nutrition of the LBW infant are not fully agreed on. Most commonly used are the accretion rates of nutrients and minerals and the resultant changes in body composition, displayed by the normally growing fetus in utero. However, there is not full agreement that these are appropriate values for all LBW infants.

Human Milk

A major advantage of the mother's milk for feeding a premature infant is the excellent psychological benefit

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this has for the mother.² She frequently feels that she has an insignificant role in the care and nurturing of her infant during the weeks or months that the baby is in the high risk nursery. By providing her own milk with its highly valuable properties, she is able to establish important bonds to her infant that may be very important in the establishment of her long-term mothering skills.

In the last six years, the nutritional qualities of the milk of the mother of the premature infant have been evaluated in a number of studies. The reports differ in many of the findings, but all agree that the milk from the mothers of premature infants is higher in protein concentration during the first four to six weeks postpartum than is the milk of mothers of term infants.3 The protein concentration in the first month and its relation to the caloric value of the milk allows the milk from their mothers to be sufficient to support good growth in many LBW infants. Milk from mothers of term infants is usually not adequate to support growth in prematures under 1500-1600 grams because of its low protein content. The reason for increased protein in milk from mothers of prematures may be the relatively low daily milk volume produced by these women.4

The fat in human milk is easily digested and absorbed by the premature infant who has reduced bile salts and pancreatic lipase levels in its duodenum. One feature of human milk, which imparts a nutritional advantage, is its content of bile salt activated lipase. This lipase begins the breakdown of the milk lipids in the premature's duodenum and, in part, substitutes for the low pancreatic exocrine secretion.¹⁵

A major advantage of milk from the infant's mother lies in the antibacterial and antiviral properties, directed particularly against the flora of the mother.⁶ These properties reside in various proteins, such as lactoferin and lysozyme, and in the secretory immunoglobulin A fraction. If the milk is taken without even a period of freezing, active macrophages in the milk may, in addition, have an important anti-infectious role in the lumen of the small intestine. Poor defense mechanisms of the premature infant against infections and the propen-

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sity of th LBW infant's intestine to suffer ischemic damage (decreased blood flow) may result in necrotizing enterocolitis. These antimicrobial factors in the mother's milk provide a system of defense against intestinal bacterial or viral replication and invasion which can significantly aid the infant's care.

The secretory immunoglobulin A, the other antiinfectious proteins and the bile salt activated lipase are proteins that are at least partially damaged by pasteurization and are extensively denatured by sterilization. Thus for human milk to provide its major benefits to the infant, it should not be heat treated. This effectively limits an infant's source for human milk to what its own mother can provide. The mother is taught how to express her milk in a clean manner and how to freeze it until she can bring it to the nursery.

Even milk from mothers of prematures has amounts of calcium, phosphorus and sodium which fall far short of what the growing premature needs. These minerals may be individually supplemented or they can be provided together with protein and other nutriets if more broad supplementation is indicated. If the premature infant is less than 1 kg, or if the mother's milk is collected more than four weeks postpartum, the protein content may be insufficient for adquate growth. In such a case, commercialy available supplements can be used or one of the premature formulas can be given in place of 1/3-2/3 of the human milk feedings each day.

The body composition of a premature fed its mother's milk more closely resembles that of a fetus *in utero* a the same post-conceptional age than does the body composition of an infant fed a cow's milk-based formula.⁷ This is perhaps the best validation of the usefulness of a program to provide mother's milk for LBW infants.

Formulas for LBW Infants

In the last ten years, the premature infant's handling of each of the major nutrients and minerals has been examined in nutritional studies. Using that information, formula manufacturers have devised formulas with types and amounts of components designed specifically for the small premature infant. Whey proteins, from cow's milk with a ratio of 60:40 to casein, are better tolerated than cow's milk proteins in a ratio of 18:32, whey to casein.8 The better tolerance is probably due to the particular amino acid constituents of the whey proteins. The amount of cow's milk protein should be in the range of 2.25-5.0 gm/Kg/d.9 The lactase enzyme activity in the intestinal mucosa is frequently low in the first weeks of life in the small premature infants, so lactose intolerance can be a cause of clinical problems in such patients. 10 To reduce the lactose load, yet provide a good caloric source while limiting the osmolality, polymerized glucose in the form of Polycose® is used in premature formulas in a ratio of 50:50 with lactose. The polymerized glucose is a good source as it is readily digested by the small premature infant.11

It has been known for many years that polyunsaturated fats from vegetable oils were digested and absorbed better by LBW infants than was butterfat. However, the small premature infant does not absorb such vegetable oil

derived fats as well as term infants because of a relatively low bile salt excretion and low pancreatic lipase excretion. Recently, medium chain triglycerides have been found to be well aborbed by the LBW infant because these fatty acids do not require the intraluminal bile salt concentrations in the duodenum needed by the longer chain fatty acids.¹² The premature formulas now contain medium chain triglycerides, as 12%-50% of the fat, with the remainder being other longer chain vegetable oils.

Small premature infants have long been known to be prone to develop osteoporosis and/or frank rickets in the first months of life. Initially, it was felt that vitamin D deficiency was the cause, but recently it has become clear that calcium and phosphorus deficiencies are at least as responsible.¹³ The rate at which the fetus normally uses calcium for bone formation is greater than the amount available in any but the most heavily supplemented formula. However, the moderate osteoporosis that develops in many rapidly growing prematures does not limit linear growth or result in bone deformities and appears to resolve by the end of the first year of life. Just how closely we should try to allow the infant to match the fetal accretion rate of calcium by heavily supplementing the formula is not yet settled.

There is current interest in adding taurine to infant formulas and to parenteral amino acid mixtures designed for use in neonates. Since taurine is a very prominent amino acid in human milk, there has been a great deal of interest in defining whether or not an essential role could be found for it in human infant nutrition. The human infant has a poorly defined, but probably very low, capacity for taurine synthesis and is dependent on milk intake for its supply of taurine. ¹⁴ Those formulas based on cow's milk protein contain very little taurine and the usual parenteral amino acid mixtures contain none.

Taurine's principal role in the human infant appears to be in the conjugation of bile acids, but large amounts are also found in the brain. Supplements of formula with taurine do not improve weight gain and do not improve fat absoption.15 However, duodenal luminal bile acid patterns are more like those of human milk-fed infants. Recently, there is evidence from work with non-human primates that taurine deficiency in infancy can result in disturbances of retinal function.16 Also, the complete lack of taurine intake seen with the usual parenteral amino acid mixtures may lead to an enhancement of the cholestatic liver disease sometimes seen in association with prolonged parenteral nutrition.¹⁷ In 1984, taurine supplementation of all of their formulas was instituted by the two major formula laboratories, Mead Johnson Laboratories and Ross Laboratories. In addition, taurine is now available in one newly introduced amino acid mixture for parenteral use (Trophamine@-McGraw Laboratories).

Docosahexanoic Acid

Another nutrient recently shown to be very important in an infant primate experimental model is the fatty acid, docosahexanoic acid, C22:6 omega 3.18 It is present in human milk and it can be synthesized in the human from another omega 3 fatty acid, linolenic acid. However, in

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the absence of linolenic acid in the diet, as can occur when safflower oil is the sole source of fat, C22:6 omega 3 deficiency can occur. This fatty acid is a major component of brain tissue and its deficiency in the infant primate leads to neurological abnormalities. Thus, the supply of omega 3 fatty acids for the LBW infant from either enteral or parenteral sources should be assured.

Parenteral Nutrition

As some infants may be receiving total parenteral nutrition (TPN) for a significant period of time, it is extremely important that the special nutritional needs of the LBW infant be met during this period. These special needs include taurine, ¹⁷ as discussed above, and perhaps also cysteine. Cysteine may be an essential amino acid in the premature infant, ¹⁹ though there is no conclusive evidence for a deficiency syndrome when it is not given.

Essential fatty acid deficiency can appear within two weeks in a small LBW infant on TPN and receiving no lipid. Parenteral lipid is commonly used both to supply essential fatty acids and to supply calories in an isoosmolal form. As with formulas for premature infants, it appears to be important that the parenteral fat contain sufficient linolenic acid to provide a substrate for synthesis of the C22:6 omega 3 fatty acid. An issue still under study is the question of whether carnitine deficiency is clinically important enough in parenterally nourished infants to warrant addition of carnitine to parenteral nutritional pareparations. Co

Summary

The results of extensive nutritional studies on all aspects of LBW infant nutrition over the last 10-15 years have been applied to the design of special formulas for premature infants. The formulas meet many of the special protein, carbohydrate, fat and mineral needs of these infants. In addition, the milk from mothers of the premature infants has proven to be nutritionally adequate for many of the infants. It has provided needed anti-infectious factors to the infants, and its use has been psychologically very important for the mothers providing it.

The field of LBW infant nutrition remains very active. Current issues include questions about the possible essential nature of taurine, cysteine, omega 3 fatty acids and carnitine in the parenteral and enteral nutrition of the premature infant. A comprehensive review of LBW nutrition will be included in the forthcoming *Pediatric Nutrition Handbook*, Second Edition, to be published by the American Academy of Pediatrics.²¹

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Dietary Iron: Chemistry and Bioavailability*

Fergus M. Clydesdale, Ph.D**

Difficulties in food iron absortion may be quantitative and/or qualitative in nature, depending upon the type of food consumed, state of iron nutriture, amount of food consumed, and other mediating factors. However, if iron is required and food intake is adequate, the problem is probably related to the type of iron in the diet, which is ultimately dependent upon the type of food consumed and the physicochemical environment provided by that food.¹

Iron is the fourth most abundant element in the earth's crust; only oxygen, silicon and aluminum are more common.² Iron ranks 26th in the periodic table and has an atomic weight of 55.85. It has several oxidation states varying from Fe+6 to Fe-² depending upon its chemical environment. The ferric form, Fe+³, and the ferrous form, Fe+², are the only states that are stable in an aqueous environment and thus are the only states that occur naturally in food. Elemental iron, Fe⁰, is rarely found in biological environments but it is a common food iron fortificant with reasonable bioavailability.³

Function

The major function of iron is to transport oxygen in the body via two transport molecules, hemoglobin in the red blood cells and myoglobin in the muscle. Hemoglobin is formed from the combination of four heme groups with one molecule of globin, while myoglobin has only one-quarter the iron the hemoglobin. Hemoglobin is responsible for oxygen transport through the entire body, while myoglobin serves as an oxygen reserve in muscle metabolism. Iron is also a component of cytochromes, enzymes (catalase, xanthine oxidase) and is involved as a cofactor of other enzyme systems, such as aconitase.

Red blood cells, the major repository for iron, die approximately every 120 days but their iron is recycled very efficiently so that little iron is excreted; losses through the urine, endogenous fecal and dermaliron loss are 0.6-1.0 mg/day. The average menstrual loss is 0.5 mg/day.

The Recommended Dietary Allowances (RDA) established by the Food and Nutrition Board in 1980 is 10 and 18 mg/day for men and women, respectively, decreasing to 10 mg for postmenopausal women.⁴

These calcultions assume an average loss of 1 mg/day in women of child-bearing age. They also assume an average absorption of 10% from the diet. This figure is

higher when extra demands are placed upon the body, such as those occurring during growth, pregnancy and lactation.

It is difficult to estimate accurately the exact amount of iron absorbed from the diet. Monsen, et al,⁵ have suggested a figure of 6 mg or iron per 1000 kcal of food in the average American diet, but this estimate does not consider the increased emphasis on dietary fiber, which is occuring in the eighties. The dramatic effect of meal constituents may be seen in a later study that categorizes iron availability into low, medium and high, depending upon the amount of meat, poultry, fish, ascorbic acid, total iron, heme iron and non-heme iron in the meal.⁶

Nevertheless, applying the estimate of 6 mg/1000 kcal, it becomes obvious that men would be able to meet their RDA quite easily, while women would have great difficulty because they would have to consume approximately 3000 kcal/day. The relationship between food intake and iron status is especially critical for certain segments of the population if few iron-enriched or iron-fortified foods are consumed or if iron supplements are not used.

Food Content and Bioavailability

In general, meats provide the greatest amount of iron in its most available form as heme iron. Non-meat sources contain non-heme iron, which is not nearly as readily absorbed due to the presence of inhibitors, such as fibers, polyphenolics, phosphates, proteins and organic acids.^{6, 7} However, these generalizations must be made with care since environmental factors in the food, such as pH, reduction potential and ligands as in organic acids and amino acids, can form soluble complexes with iron and act as enhancers of iron absroption.¹

The best known and most widely accepted enhancer of non-heme iron is ascorbic acid, but the presence of small amount of meat in the diet will also act as an enhancer. Concern about reported inhibition of iron caused by soy products prompted the International Anemia Consultative Group (INACG) to issue a monograph on the effects of cereals and legumes on iron availability.8 Their general conclusions indicated that although iron is poorly absorbed from cereals and legumes, such absorption may be increased by the inclusion of meat and/or ascorbic acid in the diet as well as by certain types of processing. Further, recent work has shown that any inhibition of iron absorption, when soy protein is substituted in beef, is partially offset by improved availability of the remaining heme iron and an increase of non-heme iron. However, conclusions concerning cereals, legumes and soysubstituted meat products must consider added requirements for infants, children and women during the reproductive years.8

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Health Implications and Status

According to dietary intake studies in the U.S., many young women are not consuming adequate amounts of iron in their diets. Half of the women, 19-50 years old, consume less than 66% of the RDA for iron; and 93% consume less than 100% of the RDA. With their lower RDA, adult men and women over 50 years old have less difficulty meeting their recommended daily intakes. A substantial proportion of children and teenagers (especially females) also are not consuming the recommended amounts of iron.¹⁰

Biochemical studies determining the extent of irondeficiency anemia in the population demonstrate the effect of the low dietary intake. Researchers estimated the prevalence of anemia in the U.S. from the results of the Second National Health and Nutrition Examination Survey (NHANES II, 1976-1980) and found the prevalence of anemia (measured as those with hemoglobin values below the 95% reference range for age and sex) to be highest in teenage girls (5.9%), young women (5.8%), infants (5.7%) and elderly men (4.4%).¹¹

There are some important health implications involved with anemia and iron deficiency. INACG has listed such problems as decreased work performance, increased risk of maternal and fetal morbidity and mortality, increased risk of infection and immunological disorders, decreased gastric juice secretion, reduced activity of intestinal cell enzymes, subcellular structural abnormalities and possible decreased growth rate.¹²

Also, iron deficiency in the absence of anemia has been found to create problems. Four groups of nonanemic, iron-deficient infants 9-12 months of age who had hemoglobin greater than 11.0 g/dl were studied. If Iron sufficiency or deficiency was based on cellular and/or biochemical evidence. Subjects in each group were tested before and after iron therapy with the Boyley Mental Development Index. Those with non-anemic iron deficiency showed a significant score increase while those with iron sufficiency or only iron depletion did not. Thus anemia is not necessarily the only criterion for biochemical alterations.

In rare cases of excess iron accumulation, the body does not excrete and/or a absorb iron normally, thus resulting in a build-up in the soft tissues that may cause cell destruction and death. Hemosiderosis is the resulting condition and is called hemochromatosis when it reaches an advanced stage. Thalassemia and sickle cell anemia are also diseases in which patients suffer from excessive iron storage.

Thus we have a situation where an optimum iron dosage must be the aim, but with the clear recognition that dangers from iron overload do exist. This is also complicated by the fact that diagnosis of anemia and iron deficiency is difficult and can be compounded by problems of variations in laboratory tests.¹⁴

Measurement of Iron Bioavailability

Available techniques for measuring the efficiency of iron absorption from oral ingestion of individual foods or ingredients have been reviewed.¹⁵ These include 1) non-isotopic in vivo techniques, such as chemical

balance, serum iron concentration and hemoglobin repletion; 2) radioisotopic in vivo methods, including extrinsic and intrinsic labeling, whole blood or hemoglobin incorporation, whole body counting, plasma labeling and isotope dilution and radioisotope balance; 3) stable isotopes and 4) in vitro methods.

Each of these has advantages and disadvantages and, in general, their results are not directly interchangeable. Smith¹⁶ has reviewed the problems presented by the environment in which the iron exists and other scientists have provided a critique of the extrinsic tag methodology.¹⁷ INACG has also discussed the applicability of certain of these methods.⁸

The in vitro techniques all depend on solubility and/or dialysis and often use pH specifications to simulate physiological conditions. However, it may be concluded that in vitro methods do not quantitatively represent in vivo experiments but often agree in a qualitative manner.

All methods suffer from the fact that iron absorption is a function of the total meal eaten and therefore it is difficult to predict bioavailability of a particular type of iron from meal to meal.

Fortification

Clearly, fortification is one of the best answers to iron deficiency anemia. In fact, Cook and Reusser have stated that "iron fortification is the optimal approach to reducing the high prevalence of iron deficiency in developing countries." 18

In developed countries, there are also examples of the efficacy of fortification. For example, studies of the prevalence of anemia among women in Sweden describe a marked decline from 30% in 1965 to 7% ten years later. ¹⁹ They estimated that 7%-8% of this decline was attributable to fortification and the rest to a combination of iron supplements, ascorbic acid intake and possibly oral contraceptives.

INACG (1977)¹² has reviewed and recommended various fortification sources and vehicles for use in developing countries and others have reviewed those fortificants which are available in the U.S.³

The choice of an iron fortification source depends upon several factors, including bioavailability, functionality in food, reactivity (type of food to be used in) and its potential chemical environment, presence of enhancers and inhibitors, type of processing and storage life.⁶, ⁷, ²⁰

The use of a very available, but reactive source, such as ferrous sulfate, does not often make sense. This is due to the fact that its reactivity will not only change the quality of the food but, in so doing, will be changed itself to a less reactive and perhaps less available compound, such as an insoluble hydroxide. In such a case, it would be much better to use a stable iron source, such as elemental iron, that would not react with the food, but would solubilize at the low pH environment of the stomach to become available.²¹

The levels used will depend upon the product and, of course, the legal limits. The latter is controlled by federal law in foods, such as flour and bread, as described in the Federal Register. 22

In addition to the previous factors, there are a number of other questions that should be answered when considering fortification: 1) Is there a need for a bioavailability standard? 2) If such a standard is developed, should it refer to the fortificant alone or as used in the processed food or in the stored processed food? 3) Should there be requirements for upper and lower amounts of absorbable iron? 4) What techniques for the measurement of bioavailability are most appropriate and cost effective?²³

It is obvious that iron nutriture is extremely important, yet not fully under stood. There are, and will be, controversies in the fortification and labeling of iron in foods. Many of these problems are not technically solvable at our present level of knowledge and will depend upon cooperation between marketers, researchers and regulatory agencies.

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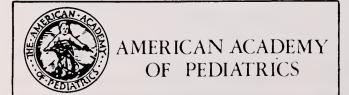
TRAUMA AS A SYMPTOM OF ALCOHOLISM

Physicians who treat trauma victims should recognize that many accidents, such as burns or falls, can be symptoms of alcoholism, according to an editorial in the March 1985 issue of *Annals of Emergency Medicine*.

Although physicians sometimes feel reluctant to obtain evidence of intoxication for fear of exposing patients to legal prosecution, the authors suggest that physicians should test for blood alcohol in "any case in which alcohol abuse may have led to accidental trauma."

Testing is critical to the early diagnosis of alcoholism, say Drs. Clark, McCarthy and Robinson, "and allows for effective treatment of the disease before irreversible damage occurs."

When patients or their refuse to acknowledge an alcohol problem exists, the authors write that "blood alcohol levels provide blunt, objective evidence that is useful to break through this wall of denial." Determining the blood alcohol level is clearly useful in rehabilitation, they say, as well as in the immediate management of alcoholism.



A TEENAGER'S PAIN: IS IT REAL OR PSYCHOSOMATIC?

Can mental concerns cause physical problems? It seems so, especially in adolescents.

"We know the mind and body are connected and people have physical reactions to emotional stresses. For example, we accept that a tension headache is stress-related. An emotional crisis can also result in physical pain," said Victor C. Strasburger, M.D.

Dr. Strasburger stressed this concept as especially important when treating adolescents. Addressing an audience at the American Academy of Pediatrics (AAP) Spring Meeting in Atlanta, Ga., he cited an example of a 15-year old patient who had severe abdominal pain for three weeks.

"Thousands of dollars worth of hospital tests all came back negative," Dr. Strasburger said. "He had been treated with numerous drugs for illnesses he didn't have.

"Nobody asked him what was going on," Dr. Strasburger continued. "He had an exactly similar episode of abdominal pain at age 12, when there was a death in his family. In fact, he was the one who found the person. He didn't go to the funeral and had no mourning period. He was hospitalized then, too, for abdominal pain, but no one noticed the connection—the three-year anniversary of the death."

A clinical professor at Yale University and director of Adolescent Medicine at Bridgeport Hospital in Connecticut, Dr. Strasburger said psychosomatic pain in definitely real. "A psychosomatic illness is not a negative diagnosis. It's something. It's just not something physical," he said.

Dr. Strasburger said a teen resents it when a doctor hints the pain is not real. "The adolescent will say, My doctors think it's all in my head." It's the doctor's fault as much as the patient's, because these patients are difficult as well as hard to diagnose. They's experiencing a dual-level pain: body and mind. They often won't admit to the secondary level, won't even listen sometimes, or they'll walk out of your office."

Dr. Strasburger stressed the importance for pediatricians—25 percent of whom care for adolescents—to ask the patient questions. "If you ask, 'How's school,' they'll say fine. But if you say, 'What kind of grades are you getting?, 'you'll get a more definitive answer. You don't ask 'How are things at home?,' but 'How do you get along with your mother?' You have to ask to know—drug use, sexual activity, parents, peers and school," he said.

The psychosomatic illness is the symptom, continued Dr. Strasburger. "The pain is really the emotional stress. Our medical technology is not sophisticated enough to pinpoint where the pain is —in the brain," Dr. Strasburger said.

And the 15-year old boy? He was referred for counseling. During the sessions, he talked about the death, wept and expressed his feelings. The abdominal pains gradually disappeared over the few weeks and in the next two years of follow-up, the pains have not recurred.

NEW DTP VACCINE SUPPLIES ALLOW RESUMPTION OF BOOSTER SHOTS

The American Academy of Pediatrics (AAP) announced that children will immediately be able to receive booster shots of the DTP (diphtheria-tetanus-pertussis) vaccine which have been deferred since December 1984.

Last December, when supplies of this vaccine were insufficient to meet demand, the AAP issued an alert to

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all parents and physicians that the shots normally administered at 18 months of age and preceding school entry would be deferred to ensure full protection of infants, the population at highest risk for pertussis. Schools, camps and day care facilities were encouraged to waive their requirements of proof of full immunization until the vaccine supply situation improved.

"It is particularly good news that the restrictions on the use of the DTP vaccine can be lifted at this time," said Martin H. Smith, M.D., AAP president-elect. "This is the season when pediatricians are getting children ready for summer camp and for the beginning of the new school year."

Until this week, only one company, Lederle Laboratories, was distributing the vaccine. Yesterday, Connaught Laboratories, which had dropped out of the marketplace in December, annouced that it is again prepared to launch full scale distribution of the vaccine, with 2.2 million doses available for immediate shipment.

Projected production schedules from Lederle, Connaught and Wyeth Laboratories, which continues to manufacture the vaccine with distribution through Lederle, indicate that supplies should be adequate to meet the needs of the nation's DTP immunization program.

Parents are advised that pediatricians will immediately resume the full DTP immunization schedule with doses administered at 2, 4, and 6 months and boosters at 18 months and preceding school entry. Further, all children whose boosters have been deferred should be scheduled to receive the doses they missed.

Dr. Smith reminded the country, and Congress in particular, that the supply of vaccines remains a fragile situation. "We need to build a minimum of six month's stockpile of *all* vaccines," he said. "This means that the government must commit adequate funding for that purpose."

He also noted that the vaccine liability situation can precipitate additional vaccine shortages at any time and urged Congress' expeditious passage of a national vaccine-injury compensation program to provide prompt and predictable justice to families whose children may suffer damage as a result of immunization.

"Unless some lasting improvement in our situation in regard to vaccine liabitity is put into place, we can expect that the improvement that we now see in our vaccine supply will certainly be temporary," Dr. Smith said.

DO WE FATTEN OUR CHILDREN AT THE TV SET? A NEW STUDY GIVES SOME STARTLING RESULTS

Two researchers have discovered what physicians have long feared —scientific links between television viewing and obesity in children and adolescents.

Even more disturbing is that the prevalence of obesity increased by 2 percent for each additional hour of TV viewed in 12 to 17 year old adolescents.

The study, published in the May issue of *Pediatrics*,

found that an association between obesity and excessive TV viewing persisted even when controlled for: prior obesity, region, season, population density, race, socioeconomic class and a variety of other family variables known to effect the prevalence of childhood obesity.

"Our findings demonstrated highly significant and reproducible associations of television watching with obesity in children and adolescents," said William Dietz, M.D., Ph.D., from the New England Medical Center, Boston, and Steven Gortmaker, Ph.D., from the Harvard School of Public Health.

The researchers studied data collected from 6,965 children, aged 6 to 11 years, and 6,671 children, aged 12 to 17 years, during two different National Health Examination Surveys from the 1960s to see if excessive fatness was associted with increased TV viewing in the United States.

The methodology provided a sample in each age group that was representative of the noninstitutionalized population of the same age and sex in the U.S.

One-third of the children studied at ages 12 to 17 had been previously examined when they were 6 to 11 years old. The surveys thus provided two cross-sectional samples and one prospective sample. Next to prior obesity, TV viewing was the most significant predictor of obesity in 12 to 17 year old adolescents.

OBESITY MEASURED BY TRICEPS SKINFOLDS

Measurements of triceps skinfolds were made by pediatricians, specially trained nurses or technicians. The triceps skinfold appears to be a more reliable measure of fatness than weight for height, the researchers said.

Obesity was defined in the study as a triceps skinfold greater than the skinfold thickness of 85 percent of children of the same age and sex.

So, how can TV be blamed for obesity in children? Children in the U.S., Drs. Dietz and Gortmaker said, spend as much time watching television as they do attending school. In 1982, children aged 6 to 11 years watched and average of 24 hours of television per week.

"Add to that the fact that food is the most heavily advertised product on children's television. Time spent viewing TV increases between-meal snacking and the consumption of foods advertised on television. But perhaps most surprising is that food consumption while watching TV may be promoted by food references in the programs themselves," the researchers said.

While either reduced energy expenditure, or increased food intake alone would not be expected to cause obesity, Drs. Dietz and Gortmaker emphasized that television is such a pervasive influence and consumes so much time that children may not be able to restore the balance between the two.

To solve this problem, the researchers observed that the prevalence of obesity could be lessened by reducing the frequency of television viewing, cutting down on food consumption while watching TV or not eating as much of the food advertised on this medium.

AEROBICS ALONE WON'T KEEP UNFIT TEENAGE BOYS FROM HIGH BLOOD PRESSURE

It is now suspected that risk factors for hypertension and heart disease begin early in one's life. A new study suggests that these risk factors can be altered in adolescence, enough to make a difference in adulthood.

The study, published in the May issue of *Pediatrics*, found that weight (as determined by body mass) provided the largest explanation for variance in risk factors such as high blood pressure, and elevated cholesterol and triglyceride counts in teenage boys. Aerobic fitness, the study concluded, contributed only minimally to reducing these risk factors.

The researchers stressed that if physical fitness programs are used to reduce risk factors, they must include a weight reduction plan. Aerobic exercise, by itself, does not vary risk factors enough for a positive change. However, the researchers said that higher levels of fitness in these boys correlated with better risk profiles.

The researchers, from the Milton S. Hershey Medical

Center and Pennsylvania State University, Hershey, and The Johns Hopkins University, Baltimore, studied 37 boys between 15 and 17 years of age. Twenty-four of the boys had a family history for hypertension or heart disease; 17 had at least one risk factor present in their lives (e.g., smoking or obesity).

The teenage boys were tenth grade students at a regional public high school and had low to moderate levels of fitness.

In children aged 6 to 10, the researchers added that it is common for fatty tissues to be present. Throughout adolescence, these tissues either increase or decrease in size. The researchers suggested that by reducing weight in a boy's teenage years, this may facilitate a healthier outlook for his adult years.

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ACTIVOS

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AIDS VIRUS ANTIBODY TEST REQUIRES CONFIRMATORY ASSAYS: STUDY

The new tests for AIDS virus (HTLV-III) antibody now being used by blood banks may be yielding unacceptably high false-positive rates, according to a study reported in JAMA. The study shows that more accurate results can be obtained by using confirmatory tests on the same samples.

James R. Carlson, PhD, of the University of California, Davis, and colleagues say that commercial tests for AIDS virus antibody are modifications of the enzyme-linked immunosorbent assay (ELISA). In their study, the researchers evaluated the sensitivity and specificity of the ELISA test on 1,257 serum samples collected from both low- and high-risk populations by confirmatory testing with the Western blot and immunofluorescence assay (IFA).

Low-risk subjects included 74 laboratory personnel and 1,014 unselected blood donors. High-risk subjects included 23 asymptomatic homosexual men, 45 hemophiliacs, 32 patients with AIDS-related complex, and 69 patients with AIDS. "Sera from six of 74 laboratory and health care personnel and 91 of 1,014 unselected blood donors were falsely positive by ELISA... based on the lack of Western blot confirmation," the researchers say. Further testing revealed only two true positives among the 1,014 blood donors, and none in the laboratory personnel.

The predictive value of a positive ELISA test result, or the percent of positives that are true positives, was much greater when testing specimens from high-risk subjects, the researchers say; 106 of the 108 with positive ELISA results also were positive by Western blot and IFA.

The Western blot and IFA tests also revealed four false-negative ELISA results, but ten of the 69 patients with AIDS had negative results from all three serological tests. The researchers note that false-positive and false-negative rates may vary among laboratories using the ELISA test, but that the consequence of maintaining a high sensitivity for the test is a loss of specificity. (A highly sensitive test will react to even a small amount of antibody, but will also produce more false-positives than a less sensitive one. A highly specific test will rarely react to anything except the particular antibody it is designed

to detect). Because of the high number of false-positive ELISA results, the researchers recommend using confirmatory tests with greater specificity, such as the Western blot and IFA, on all ELISA positive serum samples.

"The true specificity of the new commercially available and FDA-approved HTLV-III ELISA screening tests remains to be determined by the parallel testing of specimens employing confirmatory methods like Western blot and IFA," the researchers say, adding that improved antigens and reagents will eventually result in more reliable tests.

"The establishment of performance standards for the routine serological detection of antibodies to the AIDS-associated retroviruses is an urgent issue," the researchers say. Antibody to the virus has been detected in the majority (68 to 100 percent) of patients with AIDS or related conditions, as well as in 22 to 65 percent of healthy homosexual men, 56 to 72 percent of persons with hemophilia A, 87 percent of intravenous drug abusers and 35 percent of female sexual partners of men with AIDS. Antibody has been detected in less than 1 percent of persons at no known risk for AIDS.

JAMA June 14, 1985

FACTOR VIII CONCENTRATE MOST LIKELY TO TRANSMIT AIDS TO HEMOPHILIACS

Hemophiliacs who receive factor VIII concentrate have a significantly greater risk of contracting AIDS than any other blood recipient group, according to a report in JAMA. Factor VIII is used to treat persons with classical hemophilia (hemphilia A). The study found that factor IX concentrate, used to treat persons with the rarer hemphilia B, also carries a substantial, but lower risk.

It has been known for several years that hemophiliacs were at increased risk of contracting the AIDS virus, say Janine Jason, MD, of the Centers for Disease Control, Atlanta, and colleagues, but few studies have focused ont the relative risk of various blood products. They conclude that both factor VIII and factor IX concentrates may transmit HTLV/LAV, and for factor VIII recipients, positive test results for virus antibody are associated with altered immune test results.

The researchers tested for presence of antibody to the AIDS virus (HTLV III/LAV) in 234 factor VIII concentrate recipients, 36 factor IX concentrate recipients, 69 long-term recipients of frozen packed red blood cells, and 47 persons not receiving routine transfusion therapy. All participants were clinically well and had no symptoms of AIDS at the time of the testing, and except for five homosexual men, none had any other recognized risk factor for AIDS except hemophilia.

"Factor VIII concentrate recipients had a significantly higher rate of seropositivity (74 percent) than any other group," the researchers say. "Factor IX concentrate recipients had a significantly higher rate (39 percent) than recipients of frozen packed red blood cells (4 percent) or

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nontransfused persons (4 percent)." The study showed that positive antibody test results were associated with more severe hemophilia for both factor VIII and factor IX recipients; and in factor VIII recipients, seropositivity was also associated with greater factor dosage, elevated immunoglobulin, and immune complex levels, lower Thelper lymphocyte numbers, and lower ratios of Thelper to T-suppressor lymphocytes.

The researchers point out that many questions remain regarding the mechanism of HTLV-III/LAV exposure and development of AIDS. Lack of symptoms in the seropositive factor IX recipients may mean the patients are not yet immunologically compromised by the infection, or it may mean they have been effectively immunized by inactive virus. The study also showed that even seropositive factor VIII recipients with depressed T lymphocyte numbers were within the normal range. The researchers conclude that these findings may permit seropositive persons an element of optimism and should encourage researchers to search for cofactors of virus activation and/or the development of clinical AIDS. They add that since most factor IX recipients were seronegative, they represent a prime target group for AIDS prevention, through the use of heat-treated products.

The subjects in this study were from several different locations in the United States and from Vienna, Austria. Seropositivity rates for Austrian factor VIII users was significantly lower than for Americans as a whole. The researchers suggest this may be due to the lower proportion of US donors for their product. "Most of the participants receiving factor VIII concentrate manufactured all or in part from US blood donations are seropositive to one or more HTLV-III/LAV antigens," the researchers say.

JAMA June 14, 1985

DEFENSIVE LIVING (LOVING) SUGGESTED FOR SURVIVAL IN AGE OF AIDS

Changes in life style may offer the only hope for curtailing the spread of the retrovirus associated with acquired immune deficiency syndrome (AIDS), asserts George D. Lundberg, MD, editor of the *Journal of the American Medical Association*. "Individuals have the power to protect themselves more than science currently can," he says in JAMA.

Commenting on the syndrome, Lundberg says, "Not since syphilis among the Spanish, plague among the French, tuberculosis among the Eskimos, and smallpox among the American Indians has there been the threat of such a scourge. AIDS is different from any disease previously seen clinically and epidemiologically."

Among points now understood about AIDS: It is caused by a single retrovirus given three separate names; many exposed to the virus become infected; of those, 5 to 10 percent per year ultimately domonstrate symptoms; cofactors may be involved; transmission may occur years before onset of disease symptoms; antibody testing may determine who has been exposed, but does not diagnose

AIDS; a high percentage of those who develop the disease die; and there is no treatment for the immune deficiency.

Only about 2 percent of AIDS cases involve blood transfusion, Lundberg points out. The cost per case prevented through blood screening totals approximately \$2 million, he adds. "In sharp contrast, more than 70 percent of AIDS cases seem to have been transmitted sexually. Thus, until a technological method of prevention and treatment can be developed, it will be necessary to contain this virus by changing the life-style of many people —by no means all of them homosexual men. People who are infectious must stop copulating indiscrinately."

In advocating life-style changes, Lundberg points out that prevention has been accepted as an important factor in the maintenance of health. "Exercise, diet, limitations on use of tobacco and alcohol, automobile seat belts, and the like are having a major influence on the incidence of morbidity and mortality," he says. "As far as we know, prevention (of AIDS) is fairly simple," he adds.

Blood or blood products of an AIDS victim should not be injected into another person; injection needles should not be shared; AIDS patients should not become pregnant; sexual activity with an AIDS patient should not occur; and serological applicants.

Lundberg concludes: "This is a great time to practice sexual monogamy."

JAMA June 14, 1985

NEW SUBSTANCE AIDS NOSE RECONSTRUCTION

A new cartilage adhesive used in nose reconstructive surgery is deemed safe, excellent and effective in a study from New York Medical College published in the June Archives of Otolaryngology. "Enbucrilate interacts superbly well with local tissues, causing no systemic or untoward effects," reports Michael Evan Sachs, MD. In a study involving 39 patients, he found that the substance's main attribute stems from its ability to bond cartilage instantly and with great reliability, "which allows for intricate fabrication of cartilage implant components." The functional and aesthetic results in all cases were excellent.

NEW PROCEDURE TO TREAT GLAUCOMA

The first report of complete perforation of the sclera in a living human eye with the use of a laser alone appears in the June Archives of Ophthalmology. Wayne F March, MD, and colleagues from the University of Oklahoma College of Medicine in Oklahoma City describe use of the neodymium-YAG laser to test the safety of a one-step filtering procedure in an eye undergoing enucleation to remove a malignant tumor. The procedure could prove to be an effective treatment for relieving intraocular eye pressures caused by glaucoma. "Although this study was too short-term to make any long-range predictions, the

creation of a permanent filtering fistula seems more probable than with previous nonperforating procedures," the researchers say.

IMPROVED TREATMENT FOR NEONATAL CHLAMYDIAL INFECTIONS

Oral eythromycin was 93 percent effective in eradicating chlamydial infections affecting newborn infants, according to a controlled study reported in the June American Journal of Disease of Children. Alfred D. Heggie, MD, of Case Western University School of Medicine in Cleveland, and colleagues compared oral erythromycin estolate with 10 percent sulfacetamide sodium ophthalmic solution in treatment of chlamydial conjunctivitis, and found that while the former treatment was 93 percent effective, the latter was only 43 percent effective. The researchers add that use of the ophthalmic solution "may result in persistent conjunctival infection and nasopharyngeal colonization." Untreated chlamydial conjuntivitis can spread to the respiratory tract and cause chlamydial pneumonia. A genital infection, Chlamydia trachomatis can affect infants in the birthing process.

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El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse con un encabezamiento en letras mayúsculas.

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Se publicarán a discreción de la Junta Editora. Deben estar escritas en maquinilla a doble espacio, no deben ser mayores de 500 palabras, ni incluir más de cinco referencias.

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INSTRUCTIONS TO AUTHORS*

The Bulletin will accept for publication contributions relating to the various areas of medicine, surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

All authors are urged to seek clarity, brevity, and pertinence in the manuscripts regardless of subject or format.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

Manuscripts

The entire manuscript, including legends and references should be typewritten double spaced in TRIPLICATE with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgement of financial sponsors, and if the paper has been presented at a meeting the place and date should be given.

The manuscripts should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by headings in capital letters.

Articles reporting the results of clinical studies or laboratory investigation should be organized under the following headings: Introduction, Material and Methods, Results if indicated, Discussion, Summary in English and Spanish, Acknowledgments if any, and References.

Nomenclature

Generic names of drugs should be used; trade names may also be given in parenthesis, if desired. Metric units of measurement should be used preferentially).

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These should be typed on separate sheets with the title and table number Roman) centered. Symbol for units should be confined to the column headings. Vertical lines should be omitted. The language used in the tables must be the same as that of the article. Include only those tables which will enhance the understanding of the article. They should supplement, not duplicate the text.

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An abstract not longer than 150 words should accompany all articles. It must include the main points that present the core of the article and the exposition of the problem, method, results, and conclusions.

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NUESTRA PORTADA





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AGOSTO 1985

Los Extraños - Acrílico de 32" x 40" de Augusto Marín.

Augusto Marín nació en el 1921 en Santurce, Puerto Rico. Cursó sus primeros estudios con el artista español Alejandro Sánchez Felipe. En el 1946 se convierte en director artístico de Publicidad Badillo. De 1950 a 1952 es director artístico de la revista "Temas" de Nueva York y del 1954 al 1957 trabaja como director artístico de la agencia de publicidad Maz Associates. En el 1955 completa sus estudios de dibujo y pintura en el Art Student's League de Nueva York estudiando bajo la tutela de Reginald Marsh, Harry Sternberg, e Ivan Olinsky. Cursa también estudios en Los Angeles County Art Institute de California. Regresa a Publicidad Badillo en el 1958. En el 1964 estudia la técnica del vitral con el maestro Arnaldo Maas siendo becado por el Instituto de Cultura Puertorriqueña para completar sus estudio de vitral en Maastritch, Holanda.

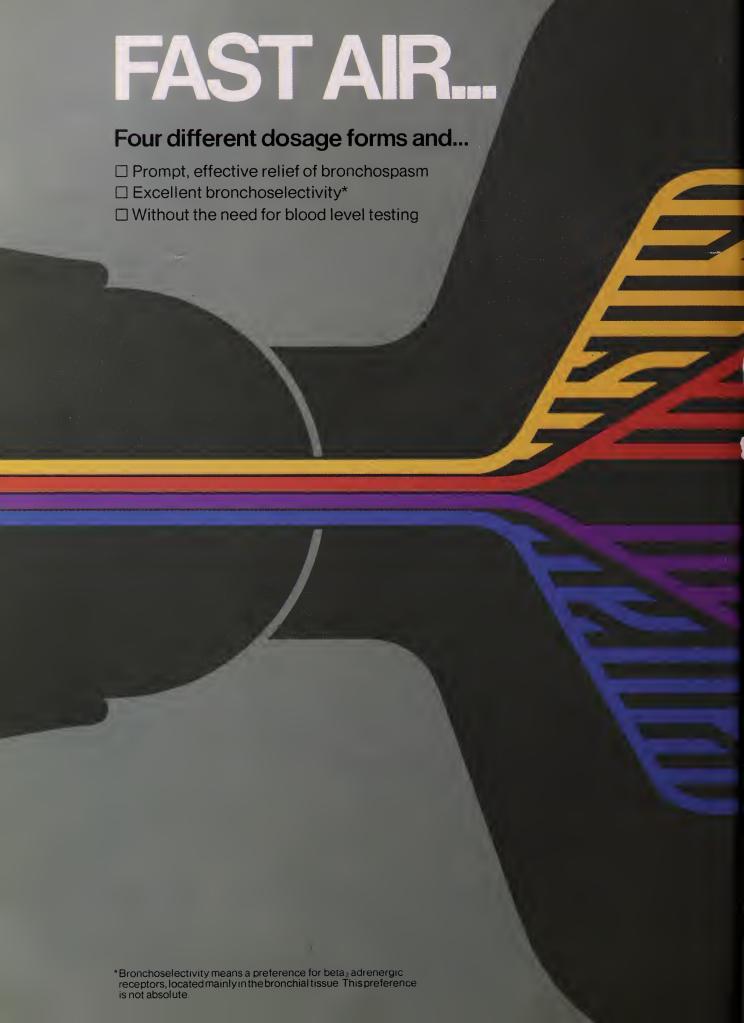
Comienza a enseñar diseño y pintura en la Escuela de Artes Plásticas del Instituto de Cultura Puertorriqueña en el 1966. Desde 1974 es profesor en el Colegio Regional de Carolina y en el 1983 cursa estudios de litografía en la Universidad de Notre Dame en Indiana.

Los seres que pueblan la naturaleza sugieren desatios a la imaginación artística. Ellos presentan a Augusto Marín un yacimiento de posibilidades que le facultan para agotar los modos figurativos tradicionales e incursionar en la búsqueda de todo tipo de distorsiones válidas. Las formas de vida en su estado original promueven en el pintor interrogantes encadenadas/orientadas a conocer las realidades prevalecientes tras las fachadas. Su máximo deleite reside en el trato con la gente. Por eso dedica gran parte de su esfuerzo artístico a extraer toda posibilidad admisible en las siluetas de sus congéneres. Las bestias

llaman su atención y repite en ellas pesquisas similares para obtener resultados equivalentes. Ese procedimiento le da visa para dilatar su expediente de alternativas con el fin de poder rebasar consistentemente sus trabajos. Utiliza ese método como antídoto contra soluciones formulistas que conducen a petrificaciones estilísticas.

Marín ha colocado su enriquecimiento intelectual al servicio de su arte. Periódicamente se registran en su obra evoluciones notables cuyos atributos responden a situaciones que se nutren del curso existencial del momento. Piensa que el proceso creativo responde a imperativos que surgen como actos de fe. Es posible que el ambiente sacramental que impregna muchos de sus lienzos provenga de la necesidad de manifestar convicciones espirituales. De esta manera, sus efectos visuales surten en el observador resultados a corto y a largo plazo. Para que sus imágenes se graben de manera indeleble en la mentes de los contempladores hace que varios factores intervengan en sus trabajos. De capital importancia es la fuerza que imprime a sus representaciones; ese procedimiento ahuyenta de ellas todo indicio de timidez. Así mismo, estudia cada mensaje a fin de convertir el soporte en parcela natural donde reside su idea. Dar permanencia a sensaciones que deben conservar su vitalidad en superficies inertes provoca tensiones entre autor y medio. El paso que le conduce a hacer sobrevivir la chispa de vida que da origen a la concepción requiere una domesticación de los materiales. Esa potestad del pintor sobre los elementos que utiliza es imprescindible para hacer reinar lo imaginativo.

La obra que aparece en la portada pertenece a la colección privada de la Dra. Ilia Ruiz Gandulla. Su reproducción ha sido posible gracias a la gentileza del autor y a la cooperación de la Sra. María Rechany de la Galería Rechany en la Calle Navarro de Hato Rey.



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References:

- Reilly, EB et al. A comparison of the onset of bronchodilator activity of metaproterenol and isoproterenol aerosols. Curr Ther Res 1974. 16 No. 8, 759-764.
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Alupent* (metaproterenol sulfate)

Bronchodilator

Tablets Metered Dose Inhaler Syrup Inhalant Solution

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Warnings: Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of Alupent, brand of metaproterenol sulfate, as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases.

Paradoxical bronchoconstriction with repeated excessive administration has been reported with other sympathomimetic agents. Therefore, it is possible that this phenomenon could occur with Alupent, brand of metaproterenol sulfate.

Patients should be advised to contact their physician in the event that they do not respond to their usual dose of a sympathomimetic amine aerosol.

Precautions: Because Alupent, brand of metaproterenol sulfate, is a sympathomimetic drug, it should be used with great caution in patients with hypertension, coronary artery disease, congestive heart failure, hyperthyroidism or diabetes, or when there is sensitivity to sympathomimetic amines

Information for Patients: Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent

Carcinogenesis: Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed

Pregnancy. Teratogenic Effects Pregnancy Category C Alupent, brand of metaproterenol sulfate, has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose and 62 times the human oral dose, the teratogenic effects included skeletal abnormalities and hydrocephalius with bone separation. Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effect at 50 mg/kg, or 310 times the human inhalation dose and 31 times the human oral dose. There are no adequate and well-controlled studies in pregnant women. Alupent, brand of metaproterenol sulfate, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when Alupent, brand of metaproterenol sulfate, is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of Alupent Metered Dose Inhaler and Inhalant Solution in children below the age of 12 have not been established. The safety and efficacy of Alupent Tablets in children below the age of 6 have not been established.

Adverse Reactions: Adverse reactions are similar to those noted with other sympathomimetic agents.

The most frequent adverse reactions to Alupent, brand of metaproterenol sulfate, are nervousness, tachycardia, tremor and nausea Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste

Overdosage: The symptoms of overdosage are those of excessive beta adrenergic stimulation listed under **Adverse Reactions.** These reactions usually do not require treatment other than reduction of dosage and/or frequency of administration.

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ESTUDIOS CLINICOS

Interaction of Third Generation Cephalosporins Combined with Amikacin Against Pseudomona Aeruginosa

Julie R. Rodríguez, M.D. Nilda I. Hernández, M.D. Carlos H. Ramírez-Ronda, M.D. Minerva Nevárez, M.T.

Abstract: Cefoperazone, cefotaxime, moxalactam and ceftizoxime were tested alone and in combination with amikacin against 20 bacteremic strains of *Pseudomonas aeruginosa*. Utilizing the FIC index the most synergistic combination was ceftizoxime and amikacin (85%). If the data is analized by the effect of the antibiotic combination on the MIC for *Pseudomonas aeruginosa*, the most active *in vitro* combination was cefoperazone-amikacin. This apparent discrepancy may be confusing; we want to alert the clinician to be careful in utilizing *in vitro* synergy data as a therapeutic guide until clinical trials are performed and the *in vitro* findings are corroborated.

Combinations of antimicrobial agents are frequently necessary to provide broad spectrum coverage in patients who are seriously ill, particularly in leukopenic and immunosuppressed patients. Pseudomonas infections are frequent in this group of patients and traditionally an aminoglycoside plus an antipseudomonal Blactam antibiotic has been used to achieve additive or synergistic antibacterial activity and/or prevent emergence of resitance.⁴, ¹²⁻¹³

In the present study the activity of four new third generation cephalosporins: cefoperazone, cefotaxime, ceftizoxime and moxalactam, alone and in combination with amikacin was tested against 20 blood isolates of *Pseudomonas aeruginosa* from compromised hospitalized patients. The study was undertaken to define the *in vitro* synergistic activity of these newer agents combined with amikacin.

Twenty strains of *Pseudomonas aeruginosa* obtained from blood cultures of hospitalized compromised patients with serious infections from the Microbiology Laboratory of the Puerto Rico Medical Center and the San Juan Veterans Administration Hospital were studied. *Pseudomonas aeruginosa* ATCC 27853 (American Type Culture Collection, Rockville, Md.) was included as control. All strains were maintained lyophilized until tested. Synergy studies were performed at least in duplicate in all isolates during a single 48-hour period.

Antibiotics. Sterile, standardized antibiotic powders were provided by their respective manufactures: cefoperazone by Pfizer Pharmaceuticals (New York, New York), cefotaxime by Hoechst-Roussel Pharmaceutical (Somerville, New Jersey), moxalactam by Eli Lilly & Co. (Indianapolis, Indiana), ceftizoxime by Smith, Kline & French Laboratories (Philadelphia, Pa.), and amikacin by Bristol Laboratories (Syracuse, New York). Specific amounts of each antibiotic were diluted in their respective solvents to prepare stock solutions with a final concentration of 1000 ug/ml.

Antibiotic combinations were prepared in microtiter plates served with the minimal inhibitory concentration (MIC) 2000 96 Channel dispenser of the Dynatech Laboratories⁷ utilizing the checkerboard pattern as previously reported.8 The range of dilutions of the Blactam agents was from 0.0625 to 64 ug/ml. Amikacin concentrations ranged from 0.25 to 16 ug/ml. On each plate one column of wells contained no B-lactam agent and one row of wells contained no amikacin. MICs of amikacin and the various B-lactam antibiotics for the 20 strains of Pseudomonas aeruginosa were read from these rows, respectively. One well per plate contained Muller-Hinton broth only to serve as a growth control. A plate with each antibiotic combination was not inoculated with organisms and served as a sterility control. All plates were kept frozen at -80° C for a maximum of two weeks prior to use.

The MIC 2000 inoculator machine inoculated 0.0015 ml of standardized suspension of approximately 3x10⁷

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CFU/ml (achieving a final inoculum concentration of approximately 4x10⁵ CFU/ml) to each well containing antibiotics. The trays were incubated at 35^oC for 18 hours and examined for bacterial growth.

The MICs of the antibiotics tested, used alone or in combination, were defined as the lowest concentration of antibiotic that inhibited visible growth.

An antimicrobial combination was defined as synergistic if there was at least a fourfold decrease in the MIC of each antimicrobial agent; and was antagonistic if there was fourfold increase in the MIC of each one of the antibiotics in the combination. All other combinations were considered indifferent.¹²

Finally, another method of quantitating synergism, the fractional inhibitory concentration (FIC) index, was calculated as previously reported. For each row in the microtiter plate, the FIC index was calculated from the lowest concentrations of drugs necessary to inhibit growth. The FIC for each drug was derived by dividing the concentration of the drug present in that well by the MIC of the organism to that drug alone. The FIC index is then the sum of these values for both drugs at that point. When the FIC index is ≤ 0.5 , the combination is synergistic; when it is > 2.0, the combination is antagonistic. If the FIC index is > 0.5, and < 2.0, the combination is indifferent. If the sum is synergistic for some combinations of concentrations and antagonistic for others, the results are considered equivocal.

Example:

MIC for *P. aeruginosa* for amikacin = 16 ug/ml MIC of *P. aeruginosa* for ceftizoxime = 64 ug/ml

No growth occurred in vitro when amikacin-ceftizoxime were utilized at 4 and 16 ug/ml, respectively. Then, the FIC index for that combination is equal to the FIC of amikacin plus the FIC of ceftizoxime. That is:

FIC index = $\frac{4}{16} + \frac{16}{64}$ FIC index = .25 + .25

FIC index = 0.5 (synergism)

All 20 strains of *Pseudomonas aeruginosa* strains were susceptible to amikacin (MIC ≤ 16 ug/ml). The first new third generation cephalosporins to have its breakpoint defined was cefotaxime.² Organisms are considered susceptible to cefotaxime or to other third generation cephalosporins if they are inhibited by a MIC of 32 ug/ml or less. Using this definition, we have that one strain of *Pseudomonas aeruginosa* was resistant to cefoperazone, 3 strains were resistant to moxalactam, 16 strains were resistant to cefotaxime and 18 strains were resistant to ceftizoxime.

Cefoperazone was the most active agent against the 20 strains of *Pseudomonas aeruginosa* tested with an MIC₉₀ of 8 ug/ml. Moxalactam, cefotaxime and ceftizoxime had comparatively similar activity with an MIC₉₀ of 64 ug/ml.

Table I compares the results of the antibiotics interaction utilizing the FIC index and the definition of synergism, antagonism and indifference as presented in methodology. Results were similar, except that by FIC index criteria, antagonism was seen in one strain of *P. aeruginosa* when amikacin was combined with cefoperazone. The MIC of this strain to amikacin increased from 4 ug/ml to 8 ug/ml (FIC index=2.003). Utilizing the definition criteria, the combination amikacin-cefoperazone was indifferent against this same strain.

By both criterias, the antibiotic combination synergistic for the greatest number of strains was ceftizoxime-amikacin. Synergism as defined by FIC index was found in 85% with the combination of ceftizoxime and amikacin. The other three combinations were comparable in activity: 20% synergism when cefotaxime or cefoperazone was combined with amikacin and 15% synergism when moxalactam was combined with amikacin.

Results of mean MIC for each antibiotic used alone and in combination with amikacin against the 20 strains of *Pseudomonas aeruginosa* are presented in Table II. When mean MICs are compared, it is observed that for cefoperazone, the mean MIC decreased onefold, from 5.6 ug/ml to 2.73 ug/ml after it was combined with amikacin. For ceftizoxime the mean MIC decreased from 43.2 ug/ml to 9.2 ug/ml (fivefold decrease); for

TABLE I

Results of antibiotic combinations againts 20 strains of
Pseudomonas aeruginosa
Combinations

		Cefoperazone Amikacin	Cefotaxime Amikacin	Moxalactam A mikacin	Ceftizoxime Amikacin
			No	o. of Stains (%)	
Synergism	FIC Index	4 (20%)	4 (20%)	3 (15%)	17 (85%)
	Definition	4 (20%)	4 (20%)	3 (15%)	17 (85%)
Antagonism	FIC Index	1 (5%)	•	-	-
, and the second	Definition	_		_	_
Indifference	FIC Index	15 (75%)	16 (80%)	16 (80%)	3 (15%)
	Definition	16 (80%)	16 (80%)	16 (80%)	3 (15%)
Equivocal	FIC Index	-	-	1	-
	Definition		-	-	_

FIC index and definition as described in methodology

moxalactam, it decreased from 21.69 ug/ml to 4.79 ug/ml (fourfold decrease); and for cefotaxime it decreased from 38.4 ug/ml to 12.03 ug/ml (threefold decrease).

TABLE II

Comparative *in vitro* activity of cefoperazone, cefotaxime, moxalactam, and ceftizoxime in combination with amikacin against 20 strains of

Pseudomonas	aeruginosa

	Antibiotic alone	Antibiotic in combination	
Antibiotic	Mean MIC	Amikacin Mean MIC (ug/ml)	Cephalosporin Mean M1C (ug/ml)
Cefoperazone	5.6	1.03	2.73
Cefotaxime	38.4	1.25	12.03
Moxalactam	21.69	1.44	4.79
Ceftizoxime	43.2	1.56	9.2
Amikacin	6.3	-	-

In a previous comparison of synergy between B-lactamtobramycin combinations, Mintz and Drew⁸ reported comparable results for cefoperazone-tobramycin (21% + 18% respectively); they also described that the cefota xime-tobramycin combination was more synergistic (63%).

Analysis of the present data is conflicting. The antibiotic combinations showing greater synergistic activity were the same ones which, paradoxically, were needed in higher concentrations as sole agents to inhibit the *P. aeruginosa* strains studied.

The combination of cefoperazone-amikacin demonstrated 20% synergism, with a mean MIC for cefoperazone as a single agent of 5.6 mcmg/ml, decreasing to 2.7 mcgm/ml when it was combined with amikacin. In contrast, while the combination ceftizoxime-amikacin demonstrated 85% synergism, the mean MIC for ceftizoxime alone was 43 mcgm/ml, and 9.2 mcgm/ml when it was combined with amikacin.

The apparent discrepancy of the *invitro* activity of the antibiotics studied when their MICs and their synergistic activity was determined, may represent a test tube effect, and may not have any clinical significance. When we study antibiotics which have very low MICs for a particular group of strains it may be very difficult to find synergism as presently defined, but then we may have to question ourselves its clinical importance or its consequences.

While we do not have answers to all the above questions, we want to bring to the attention of the clinician that *in vitro* synergy may be confusing and misleading, and although it may serve as a guide to choose an antibiotic combination, it may need controlled clinical trials before wa can safely say which is the best antibiotic combination to treat serious *P. aeruginosa* infections in the compromised host.

Resumen: Se estudió la actividad in vitro de cefoperazone, cefotaxime, moxalactam y ceftizoxime individualmente y en combinación con amikacin en contra de 20 cepas de *Pseudomonas aeruginosa* obtenidas de la sangre de pacientes.

Ceftizoxime-amikacin resultó ser la combinación más sinergística (85%) utilizando el índice de la concentración inhibitoria fraccionada (FIC index). Sin embargo, si analizamos el efecto de la combinación de los antibióticos en la concentración mínima inhibitoria (MIC) en contra de *Pseudomonas aeruginosa*, la combinación más activa in vitro lo fue cefoperazone-amikacin. Esta aparente discrepancia en los resultados puede traer confusión si no entendemos las metodologías utilizadas y lo que cada una significa. Es nuestro interés alertar al clínico y que tenga cuidado cuando utiliza el criterio de sinergismo para dirigir su terapia.

Acknowledgement

We wish to thank Mrs. Carmen D. Camareno for her excellent secretarial work.

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What can you do for hypertensives like these?



Rely on one-tablet-a-day for these and virtually

Laura K is depressed... she sleeps badly and sometimes has bad dreams. Forgetful. BP up despite medication.

Little or no depression, hallucinations, or sleep disturbances such as insomnia or nightmares have been reported with TENORMIN® (atenolol).

Paul H smokes two packs a day. Annual physical uncovered diastolic of 102 mmHg. Rigid habits ... will have difficulty with a complicated regimen.

Propranolol may produce bronchial hyperactivity in patients with no history of asthma. Smoking has been implicated-especially in males. Cardioselective **TENORMIN** exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. This preference is not

His BP is down from 172/110 mmHg to normotensive range. But Manuel G blames his medication for his impotence.

Only 0.4% of patients in the 28-day TENORMIN evaluation program reported sexual performance problems.³

At 73, Mary B is on daily insulin. Her diastolic is up 10 mmHg since last visit. Misses appointments.

Although beta

blockers may mask tachycardia occurring with hypoglycemia, TENORMIN may be tried with caution in patients with diabetes mellitus, like Mary B, who require beta blocker therapy. It does not augment insulin-induced hypoglycemia and does not delay recovery of blood same degree as

Janet M had asthma as a child but hasn't wheezed in 40 years. "Can't believe" she's hypertensive. Busy schedule demands simple regimen.
Unlike propranolol, cardioselective TENORMIN can reduce the likelihood of bronchospasm in susceptible patients. 5.6



losage and cardioselectivity all your hypertensives.

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yet another
edication.
ENORMIN is not
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mitantly with



"Real life" efficacy

These patients represent 39,745 hypertensives of all types treated effectively in the 28-day TENORMIN evaluation. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.³

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.³

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.³

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹⁰



*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute.

TENORMIN® (atendal)

See following page for brief summary of prescribing information.





Therapy for virtually every hypertensive patient in your practice.

TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN® (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2"-hydroxy-3"-[1-methylethyl) amino] propoxy]. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37° C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCI (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C). INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertendents.

sion. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

thiazide-type durete
CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater
than first degree, cardiogenic shock, and overt cardiac tailure (see WARNINGS).
WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory
function in congestive heart failure, and beta blockade carries the potential hazard of further
depressing myocardial contractility and precipitating more severe failure. In hypertensive patients
who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be
administered cautiously Both digitalis and attenoiol slow AV conduction.
In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with
heta-blocking agents over a preprod of time can in some cases, lead to cardiac failure. At the first

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn. Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN's planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihippertensive treatment. Since beta, selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta, selectivity agent (bronchodilator) made available. It dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. It treatment is continued, care should be taken when using anesthetic

the last dose and anesthesia. It treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (e.g., dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Impaired renal function (see DUSAGE AND ADMINISTERATION).

Drug Interactions: Catecholamine-depleting drugs (eg. reseptine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of closely.

of clondine.

Carcinogenesis, Mutagenesis, Impairment ot Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg /kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding. Fertility of male or fermale rats (evaluated at dose levels as high as 200 mg /kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration. Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vaculation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but

not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose,

USAGE IN PREGNANCY: Pregnancy Category C Atenolol has been shown to produce a doserelated increase in embryo / fetal resorptions in ratis at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential set to be feture. potential risk to the fetus

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving

atenolol

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eq. by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects)

teered and elicited side effects)

U.S. STUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)
CENTRAL NERYOUS SYSTEM/NEUROMUSCULAR. dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), tatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.9%), depression (0.6%-0.5%), draming (0%-0%)
GASTROINTESTINAL diarrhea (2%-0%), nausea (4%-1%)
RESPIRATORY (See WARNINGS); wheezness (0%-0%), dyspnea (0.6%-1%)
TOTALS ILS AND FOREIGN STUDIES:

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)
TOTALS U.S. AND FOREIGN STUDIES:
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM./NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), tatique (6%-5%), leithargy (3%-0.7%), drowsiness (2%-0.5%), oberression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)
GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)
MISCELLANEOUS There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolo))

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased per-

place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased per-formance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practicol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practicol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-addrenergy blocking agent are bradycardia, congestive heart failure, hypotension, brookbookenerged the proposed and the propos

dosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia. In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed TENORMIN can be removed from the general circulation by hemodialyss. In addition to gastric lavage, the tollowing therapeutic measures are suggested if warranted Bradycardia: Atropine or another anticholinergic drug Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker. Congestive Heart Failure: Conventional therapy Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis Bronchospasm: Aminophylline, isoproterenol, or atropine. Hypoglycemia: Intravenous glucose

Hypoglycemia: intravenous glucose

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a
day either alone or added to duretic therapy. The full effect of this dose will usually be seen within
one to two weeks. It an optimal response is not achieved, the dosage should be increased to

TENORMIN 100 mg given as one tablet a day increasing the dosage beyond 100 mg a day is
unlikely to produce any further benefit.

unlikely to produce any further benefit TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/1 73 m² (normal range is 100-150 ml/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1 73 m²)	Atenolol Elimination Halt-life (hrs)	Maximum Dosage	
15-35	16-27	50 mg daily	
< 15	>27	50 mg every other day	

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur. HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolot) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolot), round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

temperature

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Perfil Psicológico en los Pacientes en la Unidad de Hemodialisis del Hospital Universitario de Río Piedras

Ivonne Vicente Loperena, M.D. *
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Este estudio surge durante la rotación por la sección de consultoría y enlace del Departamento de Psiquiatría en el Hospital Universitario de Río Piedras. Nos llamó mucho la atención una serie de consultas provenientes de la unidad de hemodiálisis para evaluar pacientes que presentaban cambios de conducta y cuadros psicóticos agudos, investigar los problemas psicológicos y determinar la frecuencia de trastornos del pensamiento.

Para 1962, Brown reportó algunas de las complicaciones emocionales del procedimiento de hemodiálisis. Describió un paciente con depresión e irritabilidad.¹

En 1964, Gombos, nefrólogo, mencionó la importancia de algunos factores de estress relacionados con el proceso de hemodiálisis. Estos son la pérdida del empleo, la alteración de las actividades diarias, la falta de ingresos, la ansiedad, depresión y conducta autodestructiva.¹

El primer estudio psicológico apareció en 1965 (Shea y colaboradores) y trae una visión más amplia para su época de algunos trastornos psicológicos y su impacto en la rehabilitación del paciente. Describe 9 pacientes; dos con episodios esquizofrénicos, uno con depresión psicótica y cinco neurosis depresivas severas. Este estudio también identifica el mecanismo de defensa mayormente utilizado por estos pacientes —la negación.²

Se ha reportado que los desórdenes emocionales en los pacientes en hemodiálisis crónica son más frecuentes que en la población general y mayores en adultos que en niños.^{1, 3}

Se han reportado una serie de síntomas psiquiátricos que incluyen fobias, reacciones de ansiedad y psicosis hipománicas.⁴ Los problemas neuropsicológicos en los pacientes en hemodiálisis los podemos dividir en dos grandes grupos; aquellos relacionados con el afecto y/o pensamiento y aquellos relacionados con los procesos cognoscitivos (Tabla I).

Los problemas más comunes son la depresión y el suicidio, el pobre cumplimiento con la dieta y medicamentos y los trastornos en el funcionamiento sexual.

Existen otros equivalentes depresivos como insomnio, pérdida de apetito, prurito generalizado, dolores de cabeza; los cuales se asocian frecuentemente a trastornos

Tabla I

Problemas Neuropsicológicos en Pacientes en Hemodialisis Crónica

A. Problemas Afectivos y/o Pensamiento

Depresión Ansiedad Suicidio Prob. Libido

Hipomania Psicosis Paranoia

B. Problemas Cognoscitivos

Deficit Intelectual Síndrome de Desequilibrio Dialítico Electrónico Encefalopatía Dialítica Progresiva - (PDE) (Demencia Dialítica) Pseudodemencia

metabólicos y son difíciles de diferenciar de un proceso psicológico relacionado con la enfermedad de estos pacientes.

Armstrong³ encontró en una revisión de la literatura que el 60%, de los pacientes presentan pobre ajuste emocional. Los números fluctúan entre 0% para algunos estudios y 88% en otros. La media en su investigación es de 46%.

Encontró además que de una tercera parte a la mitad de los pacientes en un clínica no cumplen con la dieta y el régimen de tratamiento y que en algún momento del tratamiento, del 15 al 93% de los pacientes no siguen dieta.

La mayor parte del estress psicológico en estos pacientes es producto de la sensación de pérdidas múltiples. Estas pérdidas pueden ser reales, imaginarias o presentar una amenaza de pérdida.³ La depresión responde a estas pérdidas. Las pérdidas se refieren a la pérdida de la función de un órgano del cuerpo. En estos pacientes el riñón deja de cumplir su función fisiológica. Existe compromiso cardiovascular, la amenaza de fallo cardiaco congestivo es constante. Como complicación tardía tenemos neuritis periférica y osteopososis, con dificultad en los movimientos y dolor en todo el cuerpo.

Otras pérdidas corresponden a la participación en grupos sociales, la pérdida de empleo o estudios, la necesidad de posponer planes futuros y metas relacionadas con el trabajo, estudio y familia, la pérdida de autonomía y función sexual.

Otra causa de estress es la dependencia a la máquina, al personal que opera ésta y a las agencias del gobierno que pagan por el tratamiento.

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El conflicto con la dependencia a la máquina lo vemos en varias formas; aquellos pacientes muy independientes que tienen que rechazar la máquina y la dependencia a ésta y aquellos pacientes con necesidades de dependencia altas que disfrutan del proceso. En los primeros vemos hostilidad, falta a citas, pobre cumplimiento de dietas y medicamentos. En los segundos encontramos conflicto entre el tratamiento y su rehabilitación.5

El estress es mayor al enfrentarse continuamente con la muerte.

La depresión puede aparecer durante la fase urémica, ser evidente en el momento de ser aceptados al programa de hemodiálisis. Más tarde puede aparecer una segunda fase de depresión como respuesta a problemas económicos, cambios en el trabajo, dificultades maritales y sexuales y complicaciones del tratamiento o enfermedad.5,6

La depresión pues, puede ser reactiva, neurótica o psicótica. Se asocia a pobre seguimiento de dieta y medicamentos, a pobre cuidado de la fistula y trastornos cognoscitivos (pseudodemencia).6

Los mismos síntomas depresivos pueden presentarse

en pacientes con demencia encefalopática.

La incidencia de suicidios es más alta en estos pacientes. En un estudio llevado a cabo por Gordon Moore a través de los Estados Unidos, se encontró que la razón de suicidio en esta población es 400 veces mayor que en la población en general, tomando en cuenta los que mueren por no llevar a cabo tratamiento médico según indicado.⁷ Estudios más recientes llevan este número de 10 a 25 veces el de la población en general.8

Es de suponer que la reacción de cada individuo depende de las características personales antes del comienzo de la enfermedad y el tratamiento, de la edad y grado de desarrollo previo y que de estos factores depende la rehabilitación posterior.

Armstrong encontró que en Estados Unidos del 50 al 83% de los pacientes en hemodiálisis crónica mantienen un trabajo productivo y en otro estudio independiente se encontró que los pacientes que siguen vocacionalmente activos cumplen mejor con el régimen de dieta.9

La ansiedad es común en estos pacientes, aun en los que llevan más tiempo en hemodiálisis. Ocurre mayormente en respuesta al procedimiento en si.5 Muchos pacientes se quejan de trastornos en el sueño la noche anterior a recibir el tratamiento y presentan ansiedad asociada a palpitaciones y sudoración durante el proceso. Hay reportes de ataques de pánico y fobias. Algunos pacientes masculinos se masturban mientras se hemodializan.

Los casos de psicosis pueden ser de origen orgánico y/o exacerbación de un proceso funcional previo. La psicosis funcional es poco común en estos pacientes,5,6 pero puede aparecer psicosis como complicación quirúrgica o metabólica. La incidencia de psicosis tóxica en encefalopatía urémica es 2% y para cuando se presenta ya existe un cuadro delirante establecido. También puede aparecer sobreimpuesto a una demencia. Buchanan y colaboradores 10 reportaron un caso de un paciente que desarrolló un episodio de psicosis con alucinaciones visuales y delirios paranoides que luego de una evaluación exhaustiva resultó ser un trastorno orgánico perpetuado por dificultades psicológicas en el paciente.

El efecto a largo plazo sobre los procesos intelectuales no ha sido estudiado a fondo, parte del problema radica en que muchas veces no existen estudios previos al comienzo del tratamiento para comparar.

Es sabido que durante la fase urémica de la enfermedad existe dificultad en la concentración, lapsos de atención corta, trastornos en la integración viso-motora y la habilidad para abstraer. La memoria a corto y largo plazo es errática. La hemodiálisis mejora de forma temporera los problemas de atención y memoria durante los primeros doce meses de tratamiento¹¹ pero luego hay recurrencia.

En un estudio llevado a cabo por English et al¹² en un centro de hemodiálisis en Gran Bretaña utilizando una batería de pruebas psicológicas en pacientes sin evidencia de encefalopatía se encontró que, en pacientes que llevan un promedio de 3 años en diálisis la habilidad para aprender cosas nuevas estaba afectada y aumenta con el tiempo en tratamiento.

El cociente de inteligencia global no varía entre pacientes en hemodiálisis y sujetos normales.

Cabe señalar además que la ansiedad y la depresión y la preocupación con la enfermedad alteran el funcionamiento cognoscitivo.

Por último, mencionaremos dos síntomas orgánicos, uno de los cuales es motivo de consulta psiquiátrica dado los problemas de diagnóstico y manejo que representa. Estos son: el síndrome de desequilibrio dialítico y la encefalopatía dialítica progresiva.

El síndrome de desequilibrio dialítico¹¹ incluye dolor de cabeza, mareos, náuseas, calambres, irritabilidad, que puede progresar a agitación, delirio, obnubilación o convulsiones. Ocurre durante el proceso de hemodiálisis o inmediatamente después. Es de corta duración y persiste por algunos días si hay delirio presente. Se atribuye a cambios drásticos en niveles electrolíticos¹³ y por esto aparece generalmente en los inicios de la terapia. Es cada día menos frecuente debido a las mejoras en las técnicas de hemodiálisis.

La encefalopatía dialítica progresiva se caracteriza por trastornos del habla, trastornos del movimiento, trastornos cognoscitivos y trastornos del afecto y/o conducta.³

El inicio es insidioso y los primeros síntomas aparecen entre un promedio de 30 a 37 meses después de comenzado el tratamiento de hemodiálisis 11, 13, 14 aunque se han reportado casos antes del inicio de hemodiálisis y hasta después de 9 años de tratamiento.

El primer signo es usualmente tartamudeo¹¹ o alguna otra dificultad para articular palabras (disartria). La disartria es uno de los rasgos más consistentes. El paciente puede presentar mutismo o un estado de no comunicación.

El trastorno de movimiento más común es mioclonus. pero se pueden presentar muecas faciales, temblores, asterixis y debilidad muscular.6, 11, 13, 14

La demencia es global, con confusión, desorientación y trastornos de memoria y deterioro intelectual progresivo. La memoria reciente es la más alterada y puede permanecer así aún cuando el cuadro global mejore.6

Con relación a los trastornos de afecto y/o pensamiento, en estos pacientes se ha reportado euforia, irritabilidad, hostilidad, delirios paranoides y alucinaciones visuales y auditivas. La frecuencia y naturaleza es desconocida pues muy pocas veces se describe el estado mental. La demencia dialítica se puede presentar inicialmente con síntomas psiquiátricos puros.

La alteración en afecto más común es la depresión⁶ el paciente puede aparecer letárgico, apático o deprimido. La prevalencia de este síndrome es de 600 casos por 100,000 dializados (4.6%). Afecta entre 0.6 y 0.75% de los pacientes en diálisis.⁶ La edad fluctúa: ocurre igualmente en hombres que mujeres.

La causa específica no se ha establecido pero se asocia cada vez más a toxicidad por aluminio. Hasta hace poco se consideraba fatal y progresivo y sobrevenía la muerte en 24-37 meses después de su inicio (un promedio de 6 meses). Pero hay evidencia que con el manejo adecuado el síndrome puede mejorar. El diagnóstico se basa en el cuadro clínico característico junto con los cambios del electroencefalograma (EEG) y luego de descartar otros cambios que se puedan presentar como demencia (Tabla II).

Factores que precipiten o predisponen al desarrollo de esta condición lo son la hipofosfatemia, hipercalcemia, osteoporosis, uso de medicamentos que contengan aluminio, contaminación con aluminio en el agua e inmovilización.

Tabla II

Diagnóstico Clínico de Demencia Dialítica

Cuadro Clínico

Trastornos del Habla Tartamudeo, Disartria, Mutismo

Trastornos de Movimiento Muecas Faciales, Temblores, Debilidad, Mioclonos

Trastornos Cognoscitivos Confusión, Desorientación Trastornos de Memoria, Demencia

Trastornos Psiquiátricos Cambios de Conducta Depresión, Psicosis

EEG: Enlentencimiento de la Actividad Posterior

Ondas Bilaterales Sincrónicas de Predominio Frontal

Diagnóstico Diferencial

Hipercalcemia
Desequilibrio Dialítico
Hematoma Subdural
Hiponatremia
Depresión
Psicosis Funcional
Otros Trastomos Metabólicos
Pseudodemencia

Materiales y Métodos

Este estudio se Illevó a cabo en la Unidad de Hemodiálisis del Hospital Universitario de Río Piedras. La Unidad lleva doce años de operaciones y presta servicio en su mayoría a pacientes médico indigentes (Medicaid) y algunos pacientes de Medicare.

En estos mementos la unidad cuenta con 30 pacientes que reciben doce horas de tratamiento semanales dividido en dos o tres terapias.

Se incluye en el estudio los resultados obtenidos en 29 evaluaciones ya que un paciente no accedió a ser entrevistado.

La edad de los pacientes fluctúa entre 21-67 años para un promedio de 44 años (Tabla III).

Diecisiete pacientes son femeninas y doce masculinos. La edad para las pacientes femeninas fluctúa entre 21-62 años y para los varones 26-67 años. La edad promedio femenino y masculino es 44 años.

Tabla III

Datos Demográficos					
Variable	Número de Pacientes N=29	Promedic (%)			
Sexo					
F M	17 12	59 41			
Edad					
F	21-62 años	44			
M	26-67 años	44			
Estado Civil					
Casados o					
Consensual	13	44.8			
Solteros	6	20.7			
Separados	6	20.7			
Divorciados	4	13.8			
Religión					
Católica	15	52			
Evangélica	7	24			
Pentecostal	4	14			
Ninguna	3	10			
Escolaridad					
Universidad	1	3			
Superior	2	7			
Intermedia	2	7			
Elemental	11	38			
Primeros Grados	9	31			
Ninguna	4	14			
Ocupación					
Ama de Casa	11	48.3			
Desempleado	8	27.6			
Incapacidad Física	4	13.8			
Trabaja por su Cuenta	1	3.4 3.4			
Trabajo Tiempo Parcial Nada	1	3.4			
Nada	1	3.4			
Procedencia	22	70			
Rural	22	76			
Residencial Público	4	14 10			
Urbano	3	10			
Tiempo en Hemodiálisis					
(2 días a 161 meses)	.,	20			
menos de 12 meses	11	38 31			
16 a 48 meses	9	31			
más de 60 meses	9	31			

Se llevó a cabo entrevista estandarizada durante el tiempo que los pacientes se encontraban recibiendo su tratamiento de hemodiálisis. El tiempo de la entrevista fue de cuarenta y cinco minutos. Se utilizó el cuestionario de bienestar general preparado por la Doctora Luz N. Guevara, el cual a su vez incluye cuestionario de bienestar general, la escala de depresión de Beck, y el minimental para evaluación de impedimento cognoscitivo.¹⁵, ¹⁶

Se revisaron datos demográficos y médicos tales como edad, sexo, estado civil, educación, afiliación religiosa, ocupación, inicio de enfermedad, tiempo en hemodiálisis y si hubo diálisis peritoneal previa. Diagnóstico primario y otras enfermedades concurrentes.

Los trastornos investigados incluyen síntomas de ansiedad con manifestaciones autonómicas, fobias, pánico, trastornos del sueño, depresión, problema para concentrarse, ideas suicidas, trastornos del pensamiento, perceptuales, conversión, trastornos de comunicación y movimiento.

Se evaluó además el récord de cada paciente y se entrevistó el personal a cargo.

El cuestionario fue suministrado por dos residentes de psiquiatría, tercero y cuarto nivel y no teníamos conocimiento del diagnóstico primario, ni habíamos visto el récord del paciente previo a la entrevista.

Resultados

Once pacientes (37.9%) están casados, 6 pacientes (20.7%) son solteros (nunca se han casado), 6 pacientes son separados (20.7%), cuatro están divorciados (13.8%) y dos están unidos consensualmente (6.9%). En otras palabras, un poco menos de la mitad (44.8%) vive con un compañero (Tabla III).

Quince (52%) son católicos tradicionales, siete (24%) son evangélicos, cuatro (14%) son pentecostales y tres (10%) no practican religión alguna.

Con relación a su escolaridad, un paciente (3%) completó grado asociado universitario (dos años de estudios secretariales), dos completaron escuela superior (7%), dos completaron escuela elemental (38%), nueve (31%) asistieron a escuela elemental, pero no completaron y cuatro (14%) no fueron a la escuela.

Catorce mujeres (48.3%) continúan en sus labores de ama de casa con menos tareas. Ocho (27.6%) pacientes están desempleados (trabajaban antes de enfermar); cuatro pacientes reciben ayuda debido a incapacidad por causa física (13.8%). Un paciente trabaja por su cuenta (3.4%) tocando timbales, otro paciente trabaja a tiempo parcial (3.4%) y otra paciente (3.4%) reporta que en estos momentos no hace nada. Este paciente llevaba sólo dos días en hemodiálisis y su esposo realiza las tareas del hogar.

El 76% de los pacientes provienen del área rural, 14% viven en residencial público y el otro 10% proviene del área urbana.

El tiempo en hemodiálisis fluctúa entre 2 días y 161 meses.

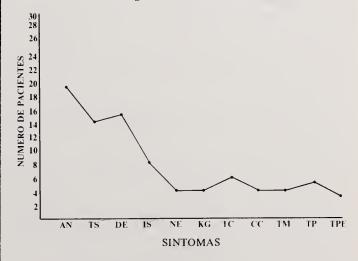
De éstos, once pacientes (38%) llevan menos de doce meses en hemodiálisis, 9 pacientes llevan entre 16 a 48 meses (31%) y los 9 restantes (31%) llevan más de 60 meses en tratamiento.

Solamente cuatro pacientes (14%) tuvieron experiencia previa con diálisis peritoneal y en su mayoría por un término menor de doce meses.

Encontramos que diecinueve (65.5%) pacientes presentan alguna queja relacionada con ansiedad. De éstos, dos la relacionan directamente con la idea de la máquina, o sea, sus síntomas aparecen durante el tratamiento o la noche anterior a asistir a su cita (figura 1).

Figura I

Perfil Psicológico del Paciente en Hemodialisis



AN Ansiedad

TS Trastornos del Sueño

DE Depresión

IS Ideas Suicidas

NE Negación

KG Impedimento Cognoscitivo

TC Trastornos de Comunicación

CC Cambios de Conducta

TM Trastornos del Movimiento

TP Trastornos del Pensamiento

TPE Trastornos de Percepción

Catorce pacientes (48.2%) presentan trastornos del sueño. Quince de los veintinueve pacientes presentan síntomas de depresión (51.7%). Una paciente refiere que estos síntomas aparecieron durante el mes antes de comenzar el tratamiento hemodialítico, o sea, durante el período urémico. Seis (40%) de estos pacientes llevan menos de 12 meses en hemodiálisis, seis (40%) llevan entre 16 a 72 meses en tratamiento y 3 (20%) más de ocho años en tratamiento.

Ocho (27%) pacientes manifiestan o han manifestado deseos de morir, ideas suicidas o intentos suicidas. Sólo uno reconoce que ha intentado quitarse la vida y este paciente en ese momento estaba psicótico.

Cuatro (13%) pacientes presentan negación, que se muestra con respuestas a las preguntas relacionadas con ideas depresivas, tales como: "el tratamiento no tiene ningún efecto sobre mi vida", "no le doy cabeza", "no pienso en la enfermedad", o "pienso curarme con este tratamiento" y "yo ni me acuerdo que tengo que venir aquí". Los cuatro tienen menos de 24 meses de tratamiento.

De toda la muestra, cuatro (13%) presentan indicadores que podrían sugerir impedimento cognoscitivo. Y de estos, dos pacientes son analfabetos y uno se negó a contestar. Dos de éstos llevan menos de cuatro meses en tratamiento. El cuarto completó séptimo grado, mostró dificultad en atención y cálculos matemáticos, memoria y lenguaje. Este lleva 9 años en hemodiálisis.

Dos (6.8%) pacientes sufren de síndrome de desequilibrio dialítico con náuseas, vómitos, hipertensión y convulsiones durante la diálisis en varias ocasiones. Uno lleva 16 meses y otro 35 meses en tratamiento.

De los 7 pacientes con más de nueve años en tratamiento cuatro han presentado (55%) o presentan trastornos de comunicación en los últimos doce meses. Estos trastornos incluyen desde no poder hablar, dificultad para hablar (disartria), no encontrar la palabra para referirse a las cosas (disnomia), disminución en el flujo del lenguaje o falta de comunicación (mutismo) y circunstancialidad.

Cuatro (55%) han presentado o presentan cambios de conducta en algún momento los últimos 12 meses y no había sido una queja presentada anteriormente durante el tratamiento.

En todos hay episodios de agresividad y uno tuvo que ser hospitalizado en el Hospital Psiquiátrico a raíz de amenazar al hijo con un cuchillo.

Cuatro (55%) han presentado trastornos del movimiento que incluyen desde episodios de parálisis en todo su cuerpo de alrededor de media hora de duración, mioclonias, tics y muecas faciales.

Tres (43%) han presentado o presentan trastornos del pensamiento en cuanto a forma o contenido. Dos pacientes presentan perseverancia, dos presentan ideas de referencia, otro bloqueo y un paciente tuvo delirios paranoides y religiosos marcados en los últimos siete meses.

Dos (22%) presentan trastornos perceptuales de contenido auditivo o visual.

En tres (43%) de estos 7 pacientes podemos constatar a través del historial y récord médico que en algún momento estuvieron fuera de contacto con la realidad y la familia o el personal médico tuvo problemas con su manejo.

Un paciente dentro de este grupo no presenta queja alguna. Este paciente lleva 10 años en hemodiálisis y cuida mucho su dieta y tratamiento. Trabaja a tiempo parcial y no presenta complicaciones secundarias por su enfermedad.

Un paciente tiene historial de abuso de polifármacos y alcohol y usa actualmente marihuana y alcohol.

Otro paciente tiene historial de abuso de alcohol hasta un mes antes de la evaluación cuando comenzó en hemodiálisis.

Además del diagnóstico primario de fallo renal crónico terminal, la variedad de problemas incluye diabetes mellitus, hipertensión arterial, riñones poliquísticos, cáncer, agenesia renal y de órganos reproductores, nefritis, glaucoma y como complicaciones al tratamiento sordera, polineuropatía, osteoporosis con fracturas espontáneas, hiperparatiroidismo secundario, fallo cardiaco congestivo y angina de pecho.

En algún momento los pacientes han presentado o pre-

sentan hipercalcemia hipo o hiperfosfatemia. Todos presentan niveles de creatinina y urea elevados pero con poca variación.

Los niveles de aluminio están elevados en todos los pacientes. Las complicaciones están relacionados con el tiempo en tratamiento.

Conclusiones

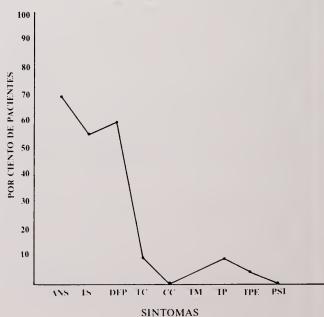
Como hemos observado, la ansiedad, los trastornos del sueño y la depresión son los síntomas más frecuentes en esta población de pacientes. Aparecen antes de comenzar el tratamiento hemodialítico asociado a desequilibrio electrolítico y uremia. Una vez comenzado el tratamiento como reacción de ajuste y a medida que surgen complicaciones durante el mismo.

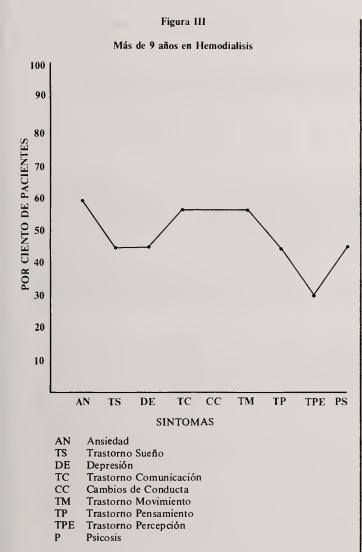
Los trastornos de comunicación, movimiento, conducta y pensamiento y los trastornos perceptuales son menos frecuentes. Sin embargo, si observamos las figuras II y III, vemos que a medida que transcurre el tiempo en hemodiálisis, éstos adquieren un lugar significativo dentro de la psicopatología de estos pacientes especialmente los que llevan más de 9 años en tratamiento.

El psiquiatra de consultoría y enlace debe estar atento a estos cambios. El énfasis de su intervención con los pacientes en el inicio de hemodiálisis debe ir encaminado hacia el manejo de los síntomas más frecuentes durante el período de ajuste. Y a medida que aumenta el tiempo en hemodiálisis se deben identificar y prevenir este segundo grupo de síntomas que presenta un problema de manejo médico y amenaza con el tratamiento efectivo del paciente.

Los factores que contribuyen para que no todos los pacientes dentro de este grupo desarrollen estos trastornos altamente sugestivos de demencia dialítica es todavía motivo de investigación.

Figura II Menos de 9 años en Hemodialisis





Observamos un paciente dentro del grupo de alto riesgo que no ha desarrollado síntomas de demencia dialítica ni complicaciones. Este paciente es el único dentro del grupo que se mantiene vocacionalmente activo. Concuerda esto con los estudios hechos por Proccis⁹ en donde encontró que los pacientes que se mantienen vocacionalmente activos cumplen mejor con su dieta.

Sabemos que un paciente bien adaptado, que entienda su enfermedad y reconozca la necesidad de seguir su régimen de tratamiento desarrollará menos complicaciones secundarias a la enfermedad y tendrá menos riesgo de desarrollar el síndrome de demencia dialítica.

Este estudio no envuelve el desarrollo pre-mórbido de estos pacientes pero reconocemos su importancia en la adaptación de éstos a las enfermedades, el desarrollo de problemas emocionales y el grado de rehabilitación que puedan adquirir.

Esta enfermedad y la particularidad de este tratamiento provee un campo vasto para la investigación de psicopatología orgánica y funcional y la utilización e investigación de los diferentes psicofármacos con que contamos en la actualidad.

El rol del psiquiatra junto con el equipo de médicos y personal a cargo del cuidado de estos pacientes es de gran utilidad para mejorar la calidad de vida de estas personas en nuestra sociedad.

Reconocimiento

Los autores desean expresar su agradecimiento al personal de la Unidad de Hemodialisis del Hospital Universitario de Río Piedras por su cooperación en este estudio.

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Monstruos, Mártires o Ejemplos: Teratología en Puerto Rico, de 1798 a 1808

José G. Rigau Pérez, M.D., F.A.A.P.

El único indicio histórico de interés local en Resumen: las malformaciones congénitas era hasta ahora el retrato de Juan Pantaleón Avilés que pintó José Campeche en 1808. Este artículo presenta además dos informes, procedentes del archivo del Real Colegio de Cirugía de San Carlos (Madrid) y hasta ahora inéditos, de casos de anormalidades congénitas en Puerto Rico. Tomándolos como base, se vislumbra cuáles serían algunas de las ideas y actitudes científicas en San Juan, de 1798 a 1808. El primer informe, redactado por Francisco Oller Ferrer, cirujano mayor del Hospital Militar de San Juan, describe un niño de dieciséis meses, con tamaño extraordinario y pulso de extremada lentitud. La explicación de Oller revela su concepción fibrilarista y vitalista de la composición del cuerpo humano. La otra disertación enviada desde Puerto Rico fue redactada en 1804 por Fray Juan José Piron, lector de artes en el convento franciscano. Describe un niño de nueve meses "que orinaba por el ombligo en donde tenía sus partes genitales" (posiblemente sufriera extrofia de la vejiga urinaria). Campeche retrató un niño sin brazos, con otras malformaciones en las extremidades inferiores, y con estrabismo. Estos informes son evidencia de que en San Juan, a finales del siglo dieciocho y principios del diecinueve, había personas técnicamente preparadas con curiosidad por las cuestiones biológicas, pero con poca propensidad a la especulación sobre causas. Estos textos son la más antigua muestra (hasta ahora publicada) de investigaciones científicas locales.

Las malformaciones congénitas has sido un tema importante en la discusión científica y filosófica por muchos siglos. La teratogénesis (en griego: "el origen de los monstruos") se ha explicado por los intelectuales como un producto de causas sobrenaturales, influencias astrológicas, impresiones mentales, la copulación entre especies diferentes, factores seminales y menstruales, y procesos fisiológicos y mecánicos. Los teólogos también

se han ocupado de explicar el sufrimiento de estas inocentes criaturas deformes, como pequeños mártires del mal, destinados a una vida de dolor. La primera autopsia en América se llevó a cabo para resolver una incógnita de índole religiosa provocada por una malformación congénita: el cuerpo de unas niñas siamesas, nacidas en Santo Domingo en 1533, ¿albergaba una o dos almas?² En el siglo dieciocho las opiniones sobre el proceso generativo estaban divididas entre dos escuelas. Los preformacionistas creían que el embrión preexistía de alguna manera en el óvulo o el espermatozoide, de forma que todos los embriones habrían sido formados por Dios en la Creación y estarían contenidos unos dentro de los otros, hasta el momento designado para su desarrollo. Los epigenesistas opinaban que cada embrión se producía através de un desarrollo gradual, partiendo de materiales que antes de la fecundación no tenían la misma organización que el embrión.³ El estudio de las malformaciones congénitas suministró ejemplos a una y otra escuela de pensamiento, aunque la aparición inesperada de un rasgo físico ajeno a ambos padres favorecía más bien los argumentos de los epigenesistas.

El eco que tuviera esta controversia en Puerto Rico se hubiera oído entre los poquísimos profesionales de la salud que tenía la isla. El único indicio de que personajes locales de esa época se interesaran en las malformaciones congénitas era hasta ahora el retrato de Juan Pantaleón Avilés que pintó José Campeche (San Juan, 1751-1809). Este artículo presenta dos informes, hasta ahora inéditos, de casos de anormalidades congénitas en Puerto Rico. Los informes proceden del archivo del Real Colegio de Cirugía de San Carlos, antecesor de la Facultad de Medicina de Madrid. Tomándolos como base, así como al cuadro de Campeche, se vislumbra cuáles serían algunas de las ideas y actitudes científicas en San Juan, de 1798 a 1808.

El Colegio de San Carlos, fundado en 1787, fue el tercero de una serie de Reales Colegios de Cirugía creados en España para elevar el nivel intelectual y social de los cirujanos en una época en que medicina y cirugía eran dos profesiones muy distintas y hasta antagónicas.

Director, División de Epidemiología, Departamento de Salud, Apartado 71423, San Juan, Puerto Rico 00936

Sus estudiantes no sólo asistían a cursos de anatomía y práctica quirúrgica, sino que también estudiaban química, botánica, fisiología, obstetricia, enfermedades de trasmisión sexual, enfermedades de los niños, y "enfermedades mixtas" que podían tener causas o remedios médicos o quirúrgicos. Los fundadores organizaron un sistema de enseñanza que combinaba los mejores libros de texto extranjeros, modernos instrumentos para laboratorios, disección y cirugía, una colección de modelos anatómicos de cera, abundancia de demostraciones por los profesores, y prácticas con los pacientes. Entre los componentes más famosos del currículo estaban las Juntas Literarias semanales, donde se relataban casos interesantes, presentados por profesores del Colegio o por cartas de corresponsales de otras regiones de España y su imperio. Una vez leída la "disertación", el director del Colegio pedía a uno de los profesores que preparara una crítica o "censura" sobre el caso y su manejo. Ocho días después se leía la censura, para discusión por los estudiantes y la facultad. Estas Juntas Literarias de los jueves permitieron a los cirujanos más distantes de la capital recibir consejos y críticas de los mejores profesores de cirugía de España. 4 En los archivos de las Juntas Literarias de San Carlos hay dos disertaciones remitidas desde Puerto Rico. La más antigua fue enviada por el cirujano Francisco Oller, y la otra tuvo como autor al monje franciscano Juan José Piron.

Francisco Oller Ferrer, cirujano mayor del Hospital Militar de San Juan, y ex-alumno del Real Colegio de Cirugía de Barcelona, firmó el 8 de octubre de 1798 una disertación sobre un niño de extraordinaria talla. La disertación, que a continuación se transcribe, llegó a la Junta de Catedráticos del Colegio de Cirugía de Madrid en 1799, y de nuevo en 1802, esta segunda vez acompañada de un retrato del niño. Su lectura pública se efectuó en la junta ordinaria del 3 de junio de 1802 pero las minutas del acto no recogen el más mínimo comentario sobre el caso. 6

Disertación

Próbida la Naturaleza en sus producciones, nos presenta desde su primer orto fenómenos que, al paso que admiran, hacen reconocer con más sólido fundamento su esencia y cualidades extrínsecas. No es necesario apelar al subterfugio del prodigio ni al enlace de causas sublunares tumultuariamente conexas y trabadas, porque lo uno es un efecto original de la superstición, y lo otro, un laberinto impenetrable erigido en la veleidad de los Atomistas, empeñada en hacer dependientes de la casualidad las cosas, y no del poder inmenso de su opífice. El Ser Supremo, por un rasgo de inmensidad y de sabiduría perfecta, dirige la naturaleza en sus funciones, y nada obra sino para exhibirnos una prueba real identificada de que no opera por un concurso simultáneo, sino por el orden conforme que ha fijado en la generación de los seres, y sus varias modificaciones. Nada nos hace más sensibles una verdad consagrada a la experiencia sino las distintas maravillas que observamos diariamente en los tres reinos animal, vegetal y mineral, en los fósiles, en el descubrimiento y curso de astros nunca vistos, y otras variaciones que advertimos en la física y la astronomía, que nos prestan a cada momento motivos justos para

admirar al mismo tiempo que para estudiar prolijamente en la Maestra del Hombre, que es la Naturaleza.

Fundado en unos principios tan incluctables (sic), jamás he perdido momento que haya podido contribuir a mi instrucción y a la común utilidad. La Humanidad siempre interesada en mis investigaciones, la he dedicado muchos instantes del ocio, y de la contemplación a mensurar con toda energía y circunspección cuanto conspira a hacerla más remarcable y menos sujeta a los males a que en su creación fue condenada. Así es que no ha llegado a mí noticia, novedad de algún aprecio, correspondiente a la Naturaleza que no haya abrigado para darla el mérito a que la hiciese acreedora una observación bien compaginada y coadunada. Entre otras que el público esparce sin otro origen que el error de un ignorante, o la afectuación de un entusiasta, llegó a mis oídos la de encontrarse en las inmediaciones de esta ciudad un niño de 16 meses cuya corporatura era asombrosa. Bastó que el informe fuese autorizado por personas graves para que tratase al punto de realizar la especie. En efecto, en 5 de octubre de este año, asociado a don Luis Rayffer, médico y cirujano titular de esta Plaza, del señor comandante de ingenieros el coronel don Tomás Sedeño, y otros sujetos de carácter, determiné visitar a este niño con la mayor prolijidad, no solo para no estar instante en la idea que había formado de sus circunstancias recomendables, sino para admirar con conocimiento práctico hasta dónde llega el Sumo Poder del Divino Arquitecto, que extrayendo del primer prototipo cuanto había de hermoso y estimable, nos ha dejado en sus trasuntos todas aquellas obras magníficas en que se complace, añadiendo algunas veces cierta cosa de extraordinario en la composición, formación y magnitud de las carnes que forma un todo el más bien unido y compacto, como si no hubiese discrimen entitativo respecto de los demás seres que ordinariamente se registran en el continente del Universo.

Relación Padres y Patria y Lugar de su nacimiento

Constituído en la mansión donde se custodiaba este pasmoso niño, que es un bohío o casa de yaguas cerca del puente de San Antonio, a media legua de distancia de esta ciudad, observé que, lejos de ser la monstruosidad que el público preconizaba, era un motivo de contemplar con estupor al advertir que la Naturaleza le había fecundado de carnes las más bien proporcionadas, y de una belleza arrogante.

Nació en 27 de mayo de 1797 en una casa de campo. Fue bautizado en la parroquia del partido de Loíza. Púsosele por nombre Juan, siendo sus padres Juan José Santo, práctico de la canal de La Habana, natural de Valencia en los reinos de España; y Alfonsa García Caniela, natural de esta isla.8

Edad, Temperamento y Corporatura de los Padres

El citado padre, Juan José, es de edad de 50 años; su temperamento, melancólico; su altura, de un hombre regular. Su madre Alfonsa, es de edad de 39 años; su temperamento bilioso; su altura mediana. Ambos declararon que la citada Alfonsa en los 22 años que llevaban de un buen matrimonio, había concebido 15 veces, de las

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cuales había tenido 4 abortos, 8 partos naturales, 2 sobre naturales [que necesitan del auxilio del arte para lograrse], 9 y éste del niño Juan, que es el sujeto de mi observación.

Cualidades y Lineamientos del Niño

El color del cuerpo de este niño es de un blanco agradable, su cutis fina, sus cabellos rubios y poblados, su frente descubierta, sus ojos pardos, la nariz proporcionada y aguileña, su boca pequeña, los labios rosados, y sus mejillas encarnadas. Se le encuentran 8 dientes incisivos, uno canino, o colmillo, y un molar. El miembro viril es pequeño, y los testículos se encuentran bien manifiestos. Sus carnes son firmes, compactas y sanas. Los huesos están bien conformados, sus articulaciones perfectamente libres, y los vasos cutáneos bien claros a la vista. Su semblante es alegre y de un atractivo muy amable.

Edad, Peso y Medida del Niño [ver figura 1]

débil, o que el sistema arterial carezca de tono por sí mismo, o bien una dilatación desmesurada, porque siendo tan lenta la circulación, no puede provenir sino del uno o del otro vicio de la organización interna.

No obstante, el niño goza al presente de todas sus facultades físicas, y todas sus funciones se hallan libres y enteramente perfectas. ¿Acaso no sería esta desplegadura tan anticipada en sus dos hermanos que murieron a los 20 meses de su edad la verdadera causa de su muerte? Sin embargo la Naturaleza en varias épocas nos ha presentado fenómenos de esta calidad, se han visto nacer muchos niños, muy corpulentos, a quienes llamaban gigantes, hijos de padres de mediana estatura, como sucede en nuestro caso, que llegaron a una edad senectudinaria, y no por eso los verdaderos filósofos han dado asento a un error vulgarizado, que es tan opuesto a sus principios y experiencias reiteradas. Sea lo que fuere de estas opiniones, la conformidad y semejanza entre este

Edad Peso y Elledida del Eviño	
	9±
	25
	8"
Circumferencia cela Cabera. 18±id Longitud cela mano.	3 ±
Hom Del Cuello 10 2 Corcum ala p. Sup. al muslo 12	5,,-,,
To del Pecho y Espaldas 23. il Hem ala pierna	_
	1

Figura 1. Edad, peso y medidas del niño Juan Santo. Biblioteca de la Facultad de Medicina, Universidad Complutense, Madrid. Memorias y censuras de las Juntas Literarias del Real Colegio de Cirugía de San Carlos. Legajo 5, 1800-1804. Disertación dei doctor Olier, folio 3.

Observación

Examinada con atención la conformación externa, observé el pulso, y en un minuto dio 52 pulsaciones sobre 96 en proporción a una persona de 35 años que disfruta de perfecta salud y de temperamento sanguíneo; en el segundo minuto dio 48 pulsaciones sobre 87 observadas en una de las hermanas del niño de edad de 6 años y de complexión biliosa, y constitución delicada; y en el tercer minuto dio 52 pulsaciones sobre 109 que observé en otra de sus hermanas de edad de 8 años y del mismo temperamento.

Juicio

Este niño no tiene el pulso tan acelerado como otro de su edad. Siendo el corazón una de las dos partes más esenciales de los vivientes, y el general motor de la máquina animal, es absolutamente necesario que tenga la fibra niño y sus hermanos hace presumir tenga la misma suerte en el curso y prolongación de su vida que los anteriores, aunque parece que la Naturaleza se rinde al exceso de su profusión cuando en una edad tan tierna se le advierten esfuerzos tan rápidos y agigantados. Esto es lo más verosímil, y no lo que supersticiosamente sienten algunos padres atribuyendo la muerte de estos sus admirables hijos a la influencia del mal de ojo y otras patrañas, invención que, sobre ser contra nuestro dogma, no debe sostenerse por serlo igualmente contra los axiomas más inconcusos de la física y de la experiencia.

Por último, este niño fue conducido a esta ciudad para que el público disfrutase de su maravillosa y estupenda corporatura, y continúa sin novedad particular en su salud. Puerto Rico y octubre 8 de 1798.

Doctor Francisco Oller"10

La estructura lógica de esta disertación es similar a la actualmente usada en la presentación de un caso interesante: preámbulo, historial familiar y personal, examen físico, y conclusiones. El preámbulo, de vocabulario que resulta ampuloso y prolijo para el lector moderno, da la clave para enmarcar el razonamiento científico del autor. Los sinónimos que Oller usa para Dios (opífice, Ser Supremo, Divino Arquitecto) son curiosos porque recuerdan el léxico de autores anatematizados por el gobierno y la Inquisición en esos años: los filósofos ilustrados, los masones y los jacobinos (Robespierre instituyó el culto al Ser Supremo). Sin embargo, las alusiones a la Creación, el pecado original y la fidelidad al dogma mantienen el texto dentro de la ortodoxia católica. Oller dice que las producciones de la Naturaleza pueden explicarse sin tener que apelar a prodigios (idea que, obviamente, sigue vigente en la ciencia moderna). No cree que los fenómenos naturales se expliquen por el "enlace de causas subluna res tumultuariamente conexas", o sea, la acción simultánea de causas materiales que coinciden por sus propias fuerzas. "La veleidad de los Atomistas", empeñada en explicar las cosas a base de la casualidad y no a base del poder del Creador, es la antecesora de lo que hoy conocemos como teoría atómica.

La idea que rechaza Oller es uno de los fundamentos de la ciencia moderna. La actitud de Oller es ambigua, a la vez materialista y con referencia a lo sobrenatural. No se debe atribuir a ignorancia o falta de curiosidad científica; al contrario, su actitud refleja las doctrinas que aprendió en sus estudios. Durante casi todo el siglo dieciocho la idea médica de la composición del cuerpo humano fue fibrilarista y vitalista. Se pensaba que las unidades básicas del cuerpo animal eran las "fibras", unidades invisibles cuya yuxtaposición longitudinal producía las fibras observables en la disección. Los procesos fisiológicas eran vistos como la actividad de una estructura anatómica movida, desde dentro de ella misma, por un específico "principio de animación" o "fuerza vital", que residía en las fibras. La figura máxima del vitalismo, el suizo Albrecht von Haller (1706-1777), fue también ardiente defensor del preformacionismo como doctrina embriológica. Al momento en que escribió Oller (1798) estas ideas seguían vigentes en Europa, aunque próximas a ser sustituídas. 11

El historial familiar del niño específica que el padre era de temperamento melancólico, mientras que la madre y las hermanas tenían temperamento bilioso. El concepto de temperamento resumía la apariencia y la personalidad del individuo. La teoría de los temperamentos se basaba, originalmente, en la teoría humoral: el humor predominante en la persona determinaba su temperamento (bilis amarilla - temperamento bilioso o colérico, bilis negramelancólico, sangre - sanguíneo, flema - flemático o linfático). Los melancólicos eran supuestamente ansiosos e irritables, con tendencia a la locura. Los biliosos o coléricos eran de complexión oscura, ojos y pelo negro, buen apetito, ágiles y moderadamente grandes de cuerpo, con rapidez de ideas, seriedad y ambición. Haller, en 1759, habiéndose ya descartado la teoría humoral, explicaba los cuatro temperamentos como el resultado de las posibles combinaciones de tono (firme o laxo) e irritabilidad (mayor o menor) de las fibras. De esta forma el temperamento melancólico del padre del niño examinado sugeriría que sus fibras eran muy laxas e irritables. El temperamento bilioso de la madre y las hermanas provendría de fibras firmes e irritables. 12

El niño tenía "carnes las más bien proporcionadas" y

"una belleza arrogante". Su examen físico demostró una apariencia sana, alegre y atractiva. Su dentición era normal, comparada con un infante de hoy, lo que quizás señala precocidad respecto a sus contemporáneos. 13 La interpretación de la tabla de medidas presenta dos dificultades: no conocemos la fiabilidad del método ni del instrumento que se utilizó al medir, y hay que convertir las unidades de medida a sus equivalencias modernas. Los símbolos utilizados para expresar el peso significan probablemente 55 libras. 14 Si, por el lugar de entrenamiento médico de Oller, escogemos las libras medicinales de Barcelona, el peso del niño hubiera sido entonces 16.5 kilos (97a percentila de peso para un niño de 24 meses). 15, 16 Considerando que la pulgada de entonces equivalía a 2.33 centímetros, las medidas de altura (86.2 cm) y circunferencia de pecho y espaldas (53.6 cm) están en, o poco sobre, la 97a percentila de los varones modernos de 16 meses.¹⁷ La circunferencia cefálica (43.1 cm) resulta menor de la segunda percentila, pero no hay por qué suponer que Oller tomó esta medida en la forma que hoy día se exige. Las medidas del ancho del pie, y la parte superior del brazo y antebrazo son desmesuradamente grandes, si no imposibles (especialmente un ancho de pie de 5.1 pulgadas modernas). La disertación dice que el niño era hermoso y proporcionado; hay que concluir que la manera de medir Oller algunas partes del cuerpo no concuerda con lo que se acostumbra hoy día (o hubo error de transcripción), y que el niño, aún hoy, nos parecería grande (en o sobre la 97a percentila), pero no monstruoso.18

Oller concluye su disertación tratando de explicar la única anomalía que ha encontrado en el niño, un pulso de extremada lentitud. Su diagnóstico diferencial incluye tres posibilidades: fibra débil, falta de tono, o dilatación desmesurada en el sistema arterial. Como ya se ha mencionado, en el siglo dieciocho se pensaba que la unidad básica de la materia animal sólida era la fibra. Las fibras débiles resultaban en vísceras y tejidos débiles, y una causa importante de esta condición era la digestión imperfecta de los alimentos. 19, 20 Pero si el niño padecía un defecto tan básico y serio como debilidad de la fibra en el sistema arterial, ¿cómo tenía un desarrollo tan "perfecto"? Oller menciona entonces por primera vez que el niño tuvo dos hermanos que murieron a los 20 meses de edad. Al lector moderno esto sugiere que quizás los tres hermanos padecieron un defecto congénito en el sistema de conducción del impulso cardíaco, aunque esos síndromes no están asociados a una corpulencia notoria.21, 22 Otra alternativa es que el niño y sus hermanos padecieran el síndrome de lipodistrofia de Berardinelli, que presenta crecimiento acelerado en la niñez temprana, y engrandecimiento de manos, pies y venas superficiales. El desarrollo notable de estos niños ocurre por hipertrofia muscular y no por gordura, pues tienen poco tejido adiposo. El síndrome también incluye engrandecimiento del falo (que en este niño no es notable), eventualmente hiperglucemia, y ocasionalmente, cardiomegalia. El patrón hereditario es autosómico recesivo, según su manifestación en progenie de matrimonios consaguíneos. 23 Para Oller, aunque "verdaderos filósofos" no habían aceptado que la corpulencia excesiva fuera necesariamente causa de muerte prematura,

"lo más verosímil" es que este niño sufriría la misma muerte prematura que sus hermanos, a causa del crecimiento rápido ("desplegadura tan anticipada") que evidencia. El cirujano rechaza vehementemente el mal de ojo como explicación de las muertes infantiles en esta familia. ¿Pensaría lo mismo el público que "disfrutó", como espectáculo, de la visita del niño a San Juan? El retrato del niño que se incluía con la disertación no está ya en la Colección anatómica del Colegio de San Carlos.²⁴ Quizás fue obra de Campeche, el artista más prolífico en San Juan en esa época.

La otra disertación enviada desde Puerto Rico a las Juntas Literarias de San Carlos señala, sorprendentemente, que no era Campeche el único en San Juan capaz de preparar una representación anatómica fidedigna. Había también un franciscano, Fray Juan José Piron, tan interesado en anatomía y tan hábil en arte que envió a los profesores una consulta ilustrada por un modelo en cera.

En la junta del 14 de noviembre de 1805 se leyó la "descripción del nacimiento de un feto muy pequeño, que orinaba por el ombligo en donde tenía sus partes genitales. Se la remitió al Señor Don Josef Ribes con un modelo de cera el Señor Don Francisco de la Cuerda desde Puerto Rico (sic); y se acordó que en la sesión inmediata se dijese lo que pareciese oportuno por los individuos de esta junta sin que se formase dictamen por escrito por no exigirlo el asunto". Al día siguiente los profesores hicieron "algunas reflexiones acerca de la descripción leída en la sesión última: y se acordó dirigir las gracias al que la remitió". 25 El memorial, transcrito a continuación, venía desde Puerto Rico, pero su autor lo envió primero al obispo de la isla, Arizmendi, quien lo envió a Francisco de la Cuerda, ex-obispo de Puerto Rico entonces residente en la Corte, para que éste lo hiciera llegar a los profesores del Real Colegio de Cirugía de San Carlos.

"Ilustrísimo y reverendísimo Señor Doctor Don Juan Alejo de Arizmendi.

El presbítero Fray Juan José Piron, religioso del Orden Seráfico, actual lector de este convento Real, tiene la satisfacción de presentar a Vuestra Señoría Ilustrísima, entre las diligentísimas contemplaciones que ha tenido y tiene en las rarezas de la naturaleza, un vivo retrato del fenómeno que ha descubierto nació en esta muy noble y leal ciudad de San Juan de Puerto Rico en la calle de la Cruz, hacia el lado del norte, el día 29 de noviembre del año próximo pasado de 1803, hijo legítimo de Don Juan Pla y Doña Juana Ximenes, su nacimiento fue a los nueve meses de su concepción, y tiene otros tantos de nacido.²⁶

Hasta ahora, Ilustrísimo Señor, nos cuentan las historias diversidad de fenómenos en toda especie de animales; pero en la racional no hemos visto, a lo menos por estos lugares, uno tan raro, y que exija más el maduro examen, entre los de la historia natural, de la Academia Española, cuyos sapientísimos maestros nos instruyan, en su vista, y nos den una exacta relación de los motivos poderosos que hayan podido ocurrir para faltar en esta parte la naturaleza a su complemento, manifestándosenos imperfectas las genitales, y fuera de su centro.

Veamos que en el mismo lugar del ombligo están por la parte de afuera los testículos, solo dentro de la túnica eritroides [fascia cremastérica], y que descansan sobre una túnica, como saco roto que a mi ver, es el periteste [túnica vaginal], que queda en figura de una repisa, como se manifiesta en el retrato. Cuando nació, aseguran sus padres, a la parte superior de los testes donde queda el ombligo, tenía un agujero por donde le cabía el dedo pulgar, éste ha ido cerrando con la carnosidad que ha brotado, y es la que se manifiesta encarnada, sobre los testículos, y solo ha dejado una abertura imperceptible en medio de aquélla por donde está en una continua evacuación de la orina. A la parte superior se ve una glandulilla, como que manifiesta señal del miembro viril; pero sin más obra que la estampada. En la parte inferior vemos una perfecta contracción del dartos; y en la superior reparamos una inflamación por todas las partes de las ingles, que manifiesta quebraduras.

Los anatómicos pueden muy bien formar un juicio prudente de las partes que se demuestren, cuáles sean los motivos de estos defectos de la naturaleza, y los que puedan concurrir para mantenerse no solo vivo, sino a un estado de convalescencia. Con este motivo, y deseando dar ocasión de más instrucción al público a expensas del dilatado estudio de los profesores y maestros, como tan apasionado a la ciencia médica, he tenido a bien dedicar a Vuestra Señoría Ilustrísima este pequeño trabajo de mi desvelo, para que como príncipe el más benévolo, y amante al progreso de las letras provoque a nuestra instrucción los fines que se indican. Puerto Rico, 31 de agosto de 1804.

Ilustrísimo y Reverendísimo Señor

A los pies de V.S.I. su más humilde súbdito, que pide a Dios dilate su importante vida en ambas felicidades por muchos años y besa sus manos.

Fray Juan José Piron

[debajo hay una nota que dice:]
Puerto Rico, 14 de enero de 1805
Aún vive el niño de que se trata, en la misma disposición.
Arizmendi''27

Fray Juan José Piron fue "lector de artes" en el convento franciscano de San Juan de 1801 a 1806.28 Al preparar un modelo de cera para los profesores, Piron les presentaba uno de los instrumentos más deseados entonces para la enseñanza de la anatomía. Los modelos de cera y marfil eran utilizados como la mejor ilustración de una realidad tridimensional que no se podía demostrar adecuadamente por la prosa científica ni el dibujo, ni por la práctica de la disección, imposible de realizar con la frecuencia necesaria por las dificultades en obtener y conservar cadáveres. Además, como ya se ha mencionado, el Colegio de San Carlos tenía especial interés en formar una buena colección de modelos de cera para la enseñanza de la anatomía a sus estudiantes.^{29, 30} La descripción anatómica que hace Piron parece correcta, pero es imposible de verificar, sin el beneficio de lo que demostraba el modelo de cera (que tampoco aparece ya en las colecciones de San Carlos). 24 Lo más probable es que el niño sufriera extrofia de la vejiga urinaria, lo cual tendría una presentación similar a lo que describe Piron, aunque sin tanta proximidad de los genitales al ombligo.^{31, 32} El monje parece muy seguro de sus conocimientos; sus preguntas a los profesores de Madrid no

son sobre anatomía. Quiere que le expliquen "los motivos de estos defectos de la Naturaleza", y los que puedan explicar la supervivencia del infante. Es una pena que la respuesta de los profesores a Piron no se incorporara a los expedientes de las Juntas Literarias. La decisión de que el asunto no exigía dictamen por escrito hace temer que la carta de respuesta en agradecimiento haya sido breve y de cumplido, una desilusión para Piron y Arizmendi, si alguna vez llegó a sus manos.

El tercer caso presentado en este artículo, a la inversa de los otros dos, consiste en una ilustración, sin disertación que la acompañe. El obispo Arizmendi mantuvo su interés por las malformaciones congénitas, y en 1808 encargó a Campeche que pintara el retrato de un niño sin brazos. El rótulo en el cuadro explica la circunstancia de la comisión:

"Juan Pantaleón hijo legítimo de Luis de Avilés y de Martina de Luna Alvarado, vecinos labradores de la Villa de Coamo en la isla de San Juan Bautista de Puerto Rico. Nació el día 2 de julio de 1806, y conducido por sus padres a esta capital, le confirió el sacramento de la Confirmación el 6 de abril de 1808 el Ilustrísimo Señor Obispo Diocesano Doctor Don Juan Alejo de Arizmendi, por cuya orden se hizo esta copia cogida del natural.

José Campeche"33, 34

Por esta inscripción se deduce que el cuadro fue pintado en abril o mayo de 1808, y es la última obra fechada del pintor que se conserva en la isla. ³⁵ El historiador de arte Arturo Dávila, en sus catálogo de obras de Campeche, indica que en América y España fueron frecuentes, durante la segunda mitad del siglo dieciocho, estos gestos de curiosidad científica de parte de los obispos en el curso de las visitas pastorales. ³⁶ Quizás la idea de Arizmendi era enviar el cuadro al Colegio de Cirugía de San Carlos, pero no hay evidencia de esa intención.

La crítica de arte Marta Traba describió el cuadro en los siguientes términos:

"El retrato es extraordinario. Apoyado en un almohadón de encajes, el torso sin brazos está rematado por una cabeza angelical, de sobrenatural belleza, signada por una tristeza irreparable a la cual contribuyen dos enormes ojos ligeramente estrábicos. Nunca la belleza del desvalimiento pudo encontrar un intérprete más elusivo y conmovedor, cuya pintura rodea lo que toca, dice sin ruido y al fin levanta el tema por sobre toda desventura."³⁷

Esta descripción resalta uno de los componentes de la destreza artística de Campeche, que es su atención a rasgos claves en la condición física de los retratados. Rel cuadro del niño Avilés es de tonos oscuros y no se puede apreciar bien en reproducciones fotográficas, pero en el dibujo aquí reproducido (figura 2) es más fácil advertir las anomalías que sufrió Juan Pantaleón: estrabismo del ojo derecho, ausencia (amelia) de ambos brazos, unión de dedos (sindactilia) y ausencia de dedos (adactilia parcial) en ambos pies. Los defectos musculo-esqueletales del niño parecen corresponder a lo que hoy se conoce como síndrome de bandas amnióticas, o bandas de constricción congénitas. En esta condición se ven ausencias únicas o múltiples de dedos de las manos o los pies, ocasional-

mente sindactilia en los dedos restantes, y a veces ausencia de una extremidad.^{39, 40} El estrabismo no forma parte de este síndrome. Muchas "amputaciones intrauterinas" ocurren porque no hay desarrollo de la parte que falta, no por la amputación mecánica de un miembro durante el embarazo. Las causas de la ausencia de extremidades son múltiples, y no están completamente dilucidadas. Es claro que pueden operar simultáneamente factores exógenos (diabetes materna, drogas como talidomida), y factores genéticos.⁴¹

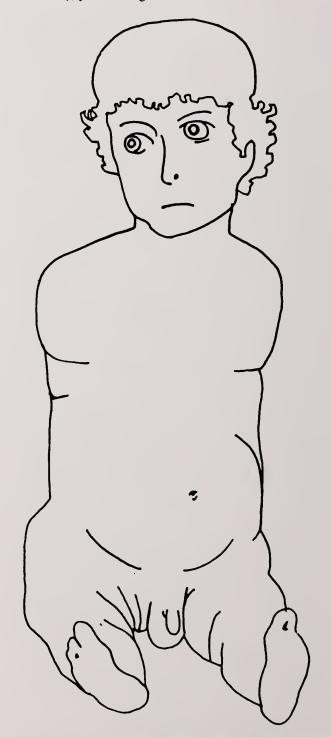


Figura 2. Juan Pantaleón Avilés. Dibujo por Juan Penabad, basado en el original de José Campeche de 1808.

Conclusión

Los documentos aquí transcritos son evidencia de que en San Juan, a finales del siglo dieciocho y principios del diecinueve, había personas técnicamente preparadas con curiosidad por las cuestiones biológicas, pero con poca propensidad a la especulación sobre causas. El interés del obispo Arizmendi en documentar los problemas de Saturnino Pla y Juan Pantaleón Avilés, y en consultar un caso con los profesores de cirugía, es un ejemplo más de la conocida compenetración del prelado con las ideas ilustradas de la época. Oller, aunque habla con estilo ampuloso de los actos del "Ser Supremo", hace descripciones detalladas y cuantificadas, y rechaza la atribución de enfermedades a prodigios o mal de ojo. Piron es aún más parco, y ni siquiera ofrece una hipótesis para explicar el caso que describe. 42 Es sorprendente hallar un escultor preocupado por cuestiones anatómicas en 1804 en el Convento de San Francisco, y surgen las siguientes preguntas: ¿por qué tenía conocimientos técnicos en anatomía? ¿dónde los adquirió? ¿son esos conocimientos una seña del nivel intelectual de los franciscanos de América a fines del siglo dieciocho? ¿enseñaba Piron anatomía en el Convento de San Francisco? ¿cómo utilizaba en el convento sus conocimientos de anatomía, sólo en enseñar arte?

Se puede especular un poco sobre las relaciones que pudo haber entre Oller, Campeche y Piron. Campeche pintó varios cuadros para Oller, entre ellos un retrato.⁴³ La conversación imaginaria durante las sesiones de pintura ha sido narrada en un cuento que confronta la personalidad de Oller, un hombre que se ha separado de su familia y lugar natal para progresar en su profesión, y la personalidad de Campeche, quien se siente responsable de mantener esos mismos lazos.44 Hay que recalcar que el autor imaginó las personalidades contradictorias (y algo anacrónicas) y luego las virtió en una idealización de Oller y Campeche; no hay evidencia directa de que ellos expresaran las opiniones que el cuento presenta. Campeche, por su continua actividad entre círculos religiosos como pintor y músico, tendría muchas oportunidades de conocer a Piron. ¿Examinó Oller el paciente descrito por el monje? Cuando nació Saturnino Pla, Oller estaba enfrascado en la introducción de la vacuna de viruela en la isla. Fue la labor que le ganó el reconocimiento general de los historiadores, pero a costa de enormes trabajos y complicaciones inesperadas, que posiblemente no le dejarían tiempo para otros proyectos.

La confrontación de las partidas de bautismo de Pla y Avilés con los documentos que describen a los niños revelan una pequeña inconsistencia (o error de transcripción) respecto a la fecha de nacimiento de Juan Pantaleón (2 de julio de 1806 según Campeche, 27 de julio según el cura). Además, aunque ambos niños sufrían anomalías severas, ninguna de las dos partidas menciona que hubiera malformación. Es obvio que las partidas de bautismo no pueden utilizarse para identificar anomalías congénitas en los bautizados. Hoy día ocurre algo parecido, pues una gran proporción de las anomalías congénitas no se menciona en los certificados de nacimiento. Agustín Stahl, en 1908, escribió que en sus años de práctica profesional había "tenido conocimiento de no pocos casos" de malformaciones. 45 Pero la experiencia clínica de un

médico tampoco da una idea fidedigna de la frecuencia del problema. Los sistemas modernos de vigilancia de malformaciones congénitas se basan en registros que activamente buscan casos, y que periódicamente autoevalúan la sensitividad y especificidad de sus métodos.

El propósito de este artículo ha sido presentar algunas de las ideas y actitudes científicas en San Juan, de 1798 a 1808, tomando como base los escritos de los investigadores originales. La explicación de los textos ha implicado una "traducción", pues los autores razonaban dentro de un idioma científico (paradigma, o sistema de teorías y conocimientos) muy distinto al actual.46 He presentado diagnósticos diferenciales con entidades nosológicas modernas, que podrían representar lo que los textos describen, con el propósito de aclarar la "traducción", y no para llegar, retrospectivamente, a juicios más acertados que los originales. La búsqueda de diagnósticos perdidos es, de por sí, un ejercicio futil, en que rara vez se puede llegar a conclusiones seguras. El proceso de ajustar el texto antiguo a los requisitos de un diagnóstico moderno fuerza a examinar con detalle el documento. Las alternativas diagnósticas que resultan de ese proceso de ajuste son interesantes, pero son un producto secundario a la comprensión del idioma científico del documento.

Estos textos son la más antigua muestra (hasta ahora publicada) de investigaciones científicas locales. No son la primera actividad científica documentada en la isla; antes hubo expediciones botánicas, como las de Sessé y Baudin en 1797, y es probable que otros médicos, cirujanos o aficionados dedicaran algún tiempo a la investigación. Sin embargo, estas disertaciones, y aún el cuadro de Campeche, son los trabajos locales de investigación más antiguos que nos restan.

Abstract: The only historical documentation of local interest in congenital malformation in Puerto Rico was, up to now, the portrait of Juan Pantaleón Avilés painted by José Campeche in 1808. This article presents, in addition, two previously unpublished case reports of congenital malformations in Puerto Rico, from the archives of the Royal College of Surgery (Madrid). Based on these reports and Campeche's painting, some of the scientific ideas and attitudes current in San Juan from 1798 to 1808 are presented. In the first case report, Francisco Oller Ferrer. chief surgeon of the San Juan Military Hospital, described a large-sized sixteen month old boy with extremely slow pulse. Oller's comments reveal a fibrillar and vitalist conception of the composition of the human body. The second dissertation from Puerto Rico was prepared in 1804 by Friar Juan José Piron, reader of arts at the Franciscan convent. It describes a nine month old boy who "urinated through the umbilicus, where his genitalia were placed" (possibly a case of exstrophy of the bladder). Campeche portrayed a boy without upper extremities, with additional malformations of the lower extremities, and with strabism. These reports provide evidence that, at the change from the eighteenth to the nineteenth century, San Juan had citizens with technical education and curiosity for biologic questions, but little propensity to speculation regarding causes. These texts are the earliest examples (published so far) of local scientific investigations.

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Before prescribing, see complete prescribing information in SK&F CO. Iterature or *POR*. The following is a brief summary.

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual, if this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amilioride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other suifonamide-derived during.

derived drugs.

Warnings: Do not use potassium supplements, dletary or other standard hypokalemia develops or dletary intake of potassium is markedly Impalred. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and dlabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in prepanacy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

appear in preast nink. In their user is essential, the putent should supriving a proper in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lipuse eythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphoterion B or corticosteroids or corticotropin (ACTH). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes meilitus. The effects of oral anticoagularist may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine ha

Diuretics reduce renal clearance of lithium and increase the risk of lithium

toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including oneumonitis and pulmonary edema, transient blurred vision, slaiadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

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Presentación de Casos

Intrathoracic Meningocele: An Uncommon Entity

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José Vargas López, M.D.
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Luis Ramírez Ferrer, M.D., F.A.C.S.
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Abstract: A middle aged Puertorrican female with an intrathoracic meningocele associated to generalized neuro-fibromatosis is presented. Recurrence and reoperation of the meningocele as well as highlights of management and technique are discussed.

The medical literature abounds with reports describing various sorts of lesions involving organs contained within the thoracic cavity. Scanty evidence is present, however, regarding the occurence of posterior mediastinal abnormalities leading to intrathoracic meningeal herniation. The infrequent occurence of this entity has prompted us to make this report. In our patient the intrathoracic meningocele was found to be present in association with generalized neurofibromatosis (Fig. 1).

Intrathoracic meningoceles have been considered to represent a faulty embryological development of the leptomeninges in their relationship with the enclosing spinal canal. Consequently they have been found to be frequently associated to spinal deformities such as scoliosis, hemivertebrae and spina bifida.

Case Report

A 43 year old female patient without history of previous systemic disease other than generalized neurofibromatosis, was found to have a left posterior mediastinal mass detected by a routine chest film taken in 1970 (Fig. 2). The patient was referred to Aguadilla District Hospital for further diagnostic tests and management.

Physical examination revealed a marked scoliosis to the left of the midline and pain in that area over the thoracic spine.

A left exploratory thoracotomy in September 1970 revealed a meningocele. It was excised and the meningeal



Figura 1. Neurofibromata and "café an lait" spots are clearly seen in the patient's back.

defect was closed with a viable pleural flap, and an uneventful postoperative course ensued. The patient remained well for the following twelve years when again chest films showed a small mass at the site of the previous excision. Due to objective progressive enlargement a myelogram was done showing recurrence of the lesion. On May 1984 the patient again underwent a left posterolateral thoracotomy and the recurring meningocele was identified, isolated and repaired. An uneventful postoperative course has been followed by no evidence of recurrence of the lesion.

Department of Surgery, Mayaguez Medical Center, University of Puerto Rico School of Medicine Consortium



Figure 2. Chest film in the AP position where a posterior mediastinal mass suggesting left hilar enlargement is seen.

Discussion

In 1882 Von Recklinghausen, at the Berlin Institute of Pathology, presented his work and description of a disease characterized by multiple tumors of the skin arising from nerve sheaths and associated with pigmentary skin changes of the, so called, "café au lait" type. He named the disease neurofibromatosis.

Generalized neurofibromatosis is a hereditary disease related to the neuroectoderm and mesoderm, having as one of its most distinct manifestations the formation of crops of skin tumors. These tumors tend to increase in size and number with advancing age.² Das Gupta and Brasfield⁵ have found in their series that 29% of these neurofibromas undergo malignant transformation. The incidence of the disease has been estimated by Prieser and Davenport⁷ to be of about one in 2000 persons. Physical signs and symptoms are usually present by 20 to 25 years of age. These nerve tumors may involve widely separated anatomical areas. Although any peripheral nerve may be affected with comparable frequency, the eighth nerve is the most frequently involved cranial nerve, with its accompanying acoustic neuroma, producing the cerebelopontine angle syndrome.4 The optic and olfactory nerves are spared of these tumor growths because of their lack of Schwann cell elements.

Ackerman and Taylor¹ found that ganglioneuromas and neurilemomas are the most common neurogenic

tumors found in the thorax. In contrast to their findings, the most common tumors of nerve origin in patients afflicted with Von Recklinghausens disease has been shown to be neurofibromas and malignant schwannomas.⁵ Benign neurofibromas are usually asymptomatic unless there is an intraspinal extension of the tumor. They usually arise from intercostal nerves. When located posteriorly in the intercostal space or at the intervertebral foramen, their slow growth may ultimately cause erosion or fracture of the vertebral pedicle with the accompanying enlargement of the intervertebral foramen. This in turn, will allow the meningeal outpouching which will usually be located in the posterior mediastinum.³ We must therefore remember that a mass in the posterior mediastinum on chest X-Ray of any patient, but specially one with Von Recklinghausens disease, may not always represent a neurogenic tumor. In 1957 Nanson⁶ reviewed the medical literature finding 27 reported cases of intrathoracic meningocele. Of these, 68% were associated with neurofibromatosis. The average age of these patients is 40 years and most of them have associated scoliosis at the level of the meningocele.

The diagnosis may be difficult, since this entity is rare when compared to the relative frequency of neurogenic tumors of the posterior mediastinum, which give identical X Ray findings on an chest film. The use of preoperative myelography constitutes a distinct help in trying to differentiate these two lesions. Although excision of the meningocele and careful closure of its neck is the treatment of choice, the preoperative knowledge of any existent intraspinal tumor component or the presence of multiple meningocele sacs is highly desirable for the surgeon. Numerous, small sized meningoceles not causing symptoms may be impossible to remove completely. In these cases it would be best to follow the patient instead of embarking on a surgical adventure of questionable benefit.

Mortality and morbidity, both surgical and on the long term, will depend upon involvement of adjacent areas like the central nervous system, skeletal, endocrine, pulmonary, etc, or the presence of malignant degeneration of these ordinarily benign tumors. It is estimated that approximately a 20% five year survival is achieved by radical surgical treatment of malignant schwannomas.

One important factor directly related to surgical mortality and morbidity is the formation of a spinal fluid fistula with the ultimate development of an empyema. Careful and meticulous surgical technique during meningeal repair as well as rapid and sustained postoperative pulmonary re-expansion should minimize these dangers.⁸, ⁹

We have followed our patient for fourteen years. In May 1984 a myelogram confirmed the suspicion of a recurrence of the meningocele in spite of the original excision and pleural flap application. At the second operation the meningeal sac was dissected out until the margins were clearly defined. It was then inverted and a Marlex mesh was applied over the defect. The surgical procedure proved to be relatively simple and the postoperative course was uneventful. Follow up has shown the patient to be asymptomatic and without neurologic sequelae.

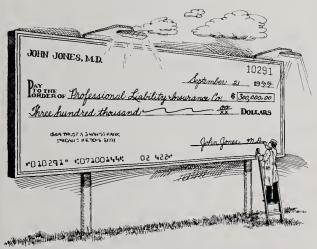
Resumen: Se presenta una paciente puertorriqueña de mediana edad con un meningocele intratorácico asociado a neurofibromatosis generalizada. La recidiva de la condición así como su reoperación con detalles técnicos son discutidos en el trabajo.

Acknowledgement

We wish to acknowledge the collaboration of George Potter, M.D., Neurosurgeon at the Mayaguez Medical Center.

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ARTICULOS ESPECIALES

Medical Malpractice — 1985*

M. Martin Halley, M.D., J.D.**

The malpractice problem is again approaching crisis proportions, impacting upon patients, competent providers, law, the insurance industry, the economy, government, and society. Primary factors, frequently obscured, are patient injuries, a by-product of modern health care, sometimes resulting from providers' negligence. The analogy to industrial injuries is apparent. The tort system, based on "fault," continues to be ineffective for reasonable and prompt compensation. The same system was condemned as anti-social and oppressive during the development of workers' compensation programs.

Innovative concepts increasingly recognize the health care injury, and compensation and assistance in rehabilitation without the proof of fault. Model programs are available in the New Zealand Accident Compensation Act, The Swedish Patient Injury Insurance Plan, and Workers' Compensation in the United States. The ultimate solution is replacement of our fault and tort law structure with an innovative no fault compensation system.

The problem of medical malpractice, more accurately referred to as medical professional liability, remains unresolved. Health care delivery crises again appear imminent, signaled by increasing claim frequency, rising claim severity, and escalating insurance premiums. Basic issues involved in the continuing controversy are generally not well understood, or may be distorted by the intensity or self interest of the parties, creating difficulty in objective evaluation. Adequate data are not easily available, so that analysis producing meaningful information for decision making is difficult.¹⁻⁵

What is the medical malpractice problem? Where does it impact? How can it be solved? These questions will be addressed in this discussion in terms of past and present development in order to identify a potential long-term solution.

The Problem

In 1971, the pervasive nature of the malpractice problem focused national attention on the subject, not due merely to the rising volume of malpractice claims, but due to concern for their potencial impact on the entire health care system. A presidential directive convened a commission on malpractice, and included the following observation: "The consequences of the malpractice problem are profound. It must be confronted soon, and it must be confronted effectively, but that will be no simple matter. For one thing, we need to know far more than we presently do about the complex problem..."

Today we do know more about the problem, but reasonable minds still differ on its precise definition. It is not primarily a problem of substandard health care practices, solvable through risk management or disciplinary action against providers. It is not primarily a controversy between physicians and trial attorneys, or between health care providers generally and the legal profession, although report and news media coverage of events may convey this interpretation. It is not primarily a problem of the insurance industry, manifested by rising premiums, although this sector is certainly involved, as are the economy, state legislatures, state regulatory agencies, and the federal government. It is primarily, however, a problem of patient injuries, real or imagined, arising out of or in the course of health care delivery, and at times resulting from health care providers' negligence.5 It is a problem of personal injury to patients in the environment of high technology-modern health care, multiple treatment modalities and drugs, an astronomical number of decisions or individual judgments for delivery or non-delivery of care, and the occurrence of suboptimal or bad results or treatment failures, sometimes in patients who formerly might not have survived.

The problem is ultimately one of society, wherein the analogy of industrial injuries to health care injuries is increasingly apparent. The former presented as a byproduct of industrialization, and because of public concern for workers and their families, resulted in legislation for the protection and compensation of workers against the special hazards intrinsic in an industrial society, first in Europe, and subsequently in the United States. The latter are an increasing hazard to patients, as

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Medical Malpractice — 1985 Bol. Asoc. Med. P. Rico - Agosto 1985

an unfortunate by-product of modern health care. Societal concern should, therefore, result in a solution providing protection and compensation—reasonable and expeditious and without the uncertainties related to determination of fault—for patients against the special risks intrinsic in health care delivery.

Historical Perspective

The Code of Hammurabi in 2250 B.C. prescribed penalities for physicians who caused loss of life, or loss of an eye. Several English malpractice cases appeared in 1700s, and the first United States case was reported in 1794. The incidence of claims was then relatively insignificant for nearly 140 years, but in the decade 1930-1940, the number of claims rose tenfold. Another tenfold increase occurred during the decade 1940-1950, and since 1950 the trend in claim frequency and severity has continued.⁷ In 1975, a national crisis in insurance availability and cost resulted in various legislative remedies involving tort law reform, frequently combined with disciplinary measures for health care providers. Liability insurance thereafter again became available. Claim frequency, severity, and insurance costs are presently escalating, and settlements, awards, or judgments in seven figures are increasingly common.

Paradoxically, the phenomenon of increasing malpractice claims and awards is occurring in a society where health care practice and achievement have attained heights previously unimaginable, and where great scientific and technological advances continue. The phenomenon is not limited to health care, but is one segment of personal injury litigation prevalent in the United States today, which includes automobile liability, product liability, air and rail liability, home owner liability, as well as professional liability generally. Medical malpractice is, therefore, a part of a general trend in tort litigation, although a number of more specific causes are as follows: diminished rapport with patients accompanying the technological and medical advances; unrealistic consumer expectations and consumer frustrations; an increasingly litigious society; an increasing number of highly skilled and increasingly specialized attorneys working in the context of the contingent fee; increasing emphasis in law school curricula upon medical malpractice; news media publicity for all kinds of medical affairs; and the influence of increasingly large awards, judgments, and settlements.

Pro-plaintiff changes in law in recent years have also been significant. These changes include abolishment of the doctrines of charitable and governmental immunity for institutions; expansion of the locality rule for medical standards and the rules for expert witness qualification; findings of oral guarantees; long statutes of limitation; liberal application of the discovery rule; application or extension of the doctrines of res ipsa loquitur and informed consent; liberalization of doctrines relating to prenatal or perinatal injury; and extension of concepts of mental suffering or emotional disturbance. Finally, proplaintiff changes include court expansion of tort law doctrines into strict liability to compensate an injured plaintiff in the absence of demonstrable fault, where the defendant, through the use of insurance, is the more

responsible person. The courts are hereby compensating individuals who suffer damages through no fault of their own by assessing damages against health care providers. Thus they "spread the risk", predicating compensation not upon the liability of an individual defendant, but upon the existence of a "deep pocket" or an insurance fund able to pay the compensation.^{8, 9}

Basis of Liability

Liability in the present tort system is frequently based on negligence although other legal theories may be applied. Negligence actions involve (1) a duty as arising out of the physician-patient relationship; (2) breach of this duty by deviation from the standard of care; (3) damage to the plaintiff; and (4) a causal relationship between the breach of duty and the damages. The legal concept of the standard is stated in court decisions as the duty of the physician to possess and exercise that degree of care and skill that is expected of a reasonably competent practitioner in the same class, acting in the same or similar circumstances. ¹⁰

The standard of care may be visualized graphically as the density function of a continuous random variable, the bell-shaped curve, a probability distribution applicable to biologic variables such as cognition, decisions, and actions. Sixty-eight per cent of behavior will fall within one standard deviation of the mean, 95 per cent within two standard deviations, and 99.7 per cent within three standard deviations. Assuming the separation of relatively good and relatively bad practice to occur at the mean, a predictable percentage of actions of decisions will be good, better, bad, or worse. Thirty-four per cent will occur within one standard deviation, 13.7 per cent will occur within one and two standard deviations, and 2.3 per cent will occur within two and three standard deviations on either side of the mean. It follows that a practitioner, no matter how knowledgeable, how competent, or how skillful, will make sub-standard decisions or perform sub-standard acts on a statistically predictable basis. The performance curve may additionally be shifted unfavorably by other circumstances such as relative congnitive ability, decisions or actions outside the practitioner's major expertise, fatigue, distraction, over-extension, behavior of assistants or others, as well as by technical, environmental, or patient factors. Even if all decisions or actions are acceptable, a number of bad results will be similarly predicatable, and "fault" may be found through application of strict liability. The bellshaped curve thus illustrates a major defect in the tort system, presenting competent practitioners with unfavorable probabilities or "negligence" and, on the other hand, requiring injured patients to prove the deviation from the mean and "fault." The combined effects of this and other defects of the tort system can be summarized as follows: there is no objective standard of liability; there is no definite measure of compensation; the entire process is susceptible to subjective considerations; the cost of litigation is high, in expenses and attorneys' fees; there is no restraint mechanism to litigation; there is no encouragement for prompt settlement; and finally, the system encourages and facilitates ever increasing awards.

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The same traditional tort system applicable to industrial injuries prior to the enactment of workers' compensation statutes was condemned as anti-social and oppressive in 1909-1910 reports to the State of New York legislature. Investigating commissions unanimously concluded that (a) a large portion of all fatal and non-fatal injuries remained uncompensated, (b) the sums actually paid were frequently inadequate token compensation, (c) recoveries were obatined only after protracted litigation, (d) the attorneys of the injured workers retained a large share of the sum actually obtained, and (e) an undue portion of the premiums paid by industry went to insurance companies for profits and administrative costs and was thus socially wasted.⁶

Impact: Health Care Consumer

Patient injuries, real or imagined, are prime factors in the malpractice problem,⁵ which is additionally affected by other causes. A number of generally beneficial recommendations have been made intended to minimize such injuries, but none can be expected to significantly abate the problem. There is no evidence that more or better education in our already lengthy health care programs, expanded disciplinary procedures against health care providers, more or better post-graduate education, increased emphasis on hospital licensing, hospital staff regulation, or other measures to encourage professional competence would have a significant impact.

In the patient's view when all is said and done, health care is a necessity and a right, but includes an inherent risk of injury. Compensation and rehabilitation must, therefore, be emphasized, but both are slow and uncertain under the present tort system. Injured patients, when compensation occurs, ultimately receive 20 per cent or less of the insurance dollar. The overall effect appears to be a wind-fall for a few patients, large rewards for a few attorneys, and income for insurance companies, defense attorneys, and others involved in the system.

Impact: Health Care Providers

The impact on health care is not only a matter of financial burden to providers, or increased cost to the public which ultimately pays both the direct costs of insurance and the indirect costs of defensive practices. The problem has been noted to touch every facet of our health care delivery system, including costs, patterns of medical practice, forms of treatment, the distribution of health manpower, the relationships between physicians and patients, and even confidence in equal justice before the law.⁵

Undesirable effects occur in the physician-patient relationship, since physicians must increasingly view each patient as a potential plaintiff. Widespread defensive practices incur additional inconvenience, cost, and risk to patients in the form of longer or earlier hospitalizations, an increased number of procedures or tests, recommendations against some procedures for legal rather than medical reasons, more consultations, early referrals to other physicians, stricter limitation of

practice, withdrawal from emergency service, or early retirement of experienced physicians. Another significant problem may be physician dysfunction subsequent to the filing of a claim, or during trial. On the other hand, beneficial effects of defensive practices have been noted, since these may also be good patient care, and quality control benefits for health care through the threat of tort litigation have been suggested.

Yet another area of impact is the increasing participation by physicians or other health care providers in claim review for attorneys or as medical witnesses. A recent estimate based on analysis of national advertising material indicates that 3000 physicians are active in this process. Remuneration is substantial: \$500 for chart review, analysis or report; \$600 for depositions; and \$3000-\$5000 daily, plus expenses for court appearances. Thus the alleged medical "conspiracy of silence"—once a chronic complaint of the legal profession concerning difficulty in obtaining medical witnesses—has been replaced by vigorous market place activity, with numerous physicians competing for the opportunity to participate in a lucrative field. Availability of abundant medical testimony and assistance in case preparation is believed to be one of the catalysts that has opened the floodgate of professional liability litigation in the medical field.11

Impact: The Legal System

The legal system, consisting of attorneys, courts and law, has been a fundamental factor in the present malpractice problem, most importantly through the expansive application of the fault and liability concepts of tort law. Attorneys and judiciary will continue to be important in the developing efforts to restructure the tort system, and can be expected to resist change in terms of fault, liability, adversary and litigation, concepts deeply ingrained in Anglo American law. Law students and attorneys are firmly attached to the adversarial process which requires parties to "battle" to reach truth and justice, a process that essentially renders only a victor. Law students and attorneys are less familiar with the terms negotiation, settlements, mediation, and compensation without fault. Therefore, the "fault" frame of reference continues to be the legal profession's response to many societal problems, as contrasted to the "compensation" system based on a foundation other than "fault."¹²

Certain other factors involving the legal system deserve mention. The increasing number of attorneys-which has resulted in manpower for specialization and increasing expertise—has been suggested as a major factor in the escalation of the malpractice problem. Attorneys—both plaintiffs and defense—with special interest in this field, contribute not only time and skill to legal issues, but exercise considerable legislative influence to actively or passively oppose changes in a framework that has identified health care with other major target defendants. The legal system thus professes to protect the rights of patients and strives for injury compensation within the present tort law, but these objectives are at times obscured by seemingly inappropriate tort law results, as well as by highly visible controversies involving opposition to legislative reforms of tort law structure.

Impact: Insurance

The insurance industry at the time of the 1975 crisis was in a state of near collapse, manifested by carrier withdrawal from the marketplace and by increasing premiums. State legislatures then enacted a variety of tort law modifications, and frequency of claims declined for three years, but claim severity continued to increase. In the 17 states where a financial limitation was placed on awards, and in the 16 states where the collateral source rule was repealed or modified, claim severity was reduced, but no effect on frequency was noted. No other substantive legal reform was found to have statistical significance in reducing either the frequency or the severity of claims.¹³

In Kansas, the Health Care Stabilization Fund, established in 1976 under the Health Care Providers' Insurance Availability Act, was intended to be accompanied by a limitation on total awards. 14, 15 The limitation, however, was never seriously considered by the legislature, and by 1983 the fund was actuarially insolvent. Legislative intervention was required: basic insurance coverage requirement was increased, excess coverage available from the fund was limited, and the levey of the fund surcharge was changed to an accrual basis. As a result, health care providers' insurance premiums increased substantially.

The Kansas Insurance Department reported on June 30, 1984, that awards against the fund totaled \$22,222,605 Ninety-five awards had been paid with an average payment of \$233,912. A total of 710 cases had been filed, and 365 remained active. Most significantly, there had been eight claim awards, judgments, or settlements in the million-dollar range in the past 15 months. The increasing exposure of the fund, together with a continuing unfunded liability, may necessitate additional corrective legislation, as well as studies of insurance alternatives to its continuation.

Impact: Economy

The economic impact of malpractice is difficult to measure, although it is generally believed to be substantial. Present emphasis on health care cost-control focuses attention on this aspect of an industry accounting for 10.9 per cent of the gross national product. A 1983 report¹¹ estimated direct annual malpractice costs—the insurance premiums paid by physicians—as \$1.75 billion, but could not estimate hospital premium costs, which included liability premiums, risk management programs, and other miscellaneous items. Indirect costs, attributed to defensive medical practices, were estimated as \$15.1 billion, but a number of these practices may not be strictly defensive. Current direct costs are reported as \$3.5 billion, and indirect cost estimates ranges up to 30 per cent of total health care expenditures.

Impact: Government

State legislatures have been, and continue to be, the arena where reforms must be obtained, but remedies have been variable and have not resulted in a long-term solution. In Kansas and other states, legislation has produced only "piecemeal" reforms that have princi-

pally resulted in continuing availability of liability insurance.

The current legislative program of the Kansas Medical Society again consists of tort reform proposals. It will include proposals for limitation of total awards, limitation of pain and suffering, collateral source revision, modification of attorney's fees, itemization requirements for verdicts, reduction of the judgment interest rate from the current 15 per cent, allowing periodic payments to expire at the death of a plaintiff, and a procedure providing incentive to early settlement. Legislative consideration of these proposals will require concerted action by health care providers, including coalitions with other interests affected by present tort liability problems. Other requirements are general agreement on the program and its objectives, adequate funding, news media exposure, public education, legislative information programs, individual contacts with legislators, and perhaps a governor's task force to address important

At the federal level, interest in medical malpractice is inevitable, since the government is the largest single purchaser of health care services. In the past, this interest has been passive, but in April 1984, an "Alternative Medical Liability Act" was introduced in the House by Representatives Moore and Gephart, 17 incorporating previously published recommendations, 16 and was referred to the Committee on Ways and Means. This bill provided for settlement of malpractice claims arising in programs established under federal law. The central feature permitted a health care provider potentially liable for personal injury to tender compensation for the claimant's net economic loss, and by this act, to foreclose tort law litigation.

Medical opposition to the bill focused on its doubtful effect on defensive medical practices, the possible cost impact of an increased number of claims, problems of court involvement, and issues related to provider decisions, third party joinders, and federal intervention. The appearance of these concepts at federal level may signal a more active posture, and may serve to encourage state solutions in the hope of avoiding further federal action.

Discussion

Efforts to resolve the malpractice problem in the United States have generally involved insurance alternatives or tort law modification, as well as recommendations for preventive action in the health care industry. Insurance programs are of obvious importance, since availability and reasonable premium structure are essential to continuing health care practice. Tort law modification has been difficult to obtain, and has not proven significantly effective, since available data indicate that only total award limitation and collateral source modification have produced measurable short term mitigation. Preventive programs are important, but an irreducible number of injuries will nevertheless occur.

Innovative concepts are, therefore, assuming increasing significance. Their overall thrust is the evolving recognition of the health care injury arising out of

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modern health care delivery, and the increasing consensus that compensation for such injury, and assistance in rehabilitation, should not depend upon the proof of fault. 18-21 Definition of the injury, or compensable event, continues to be the major challenge in several available studies. 22, 23 Initial concerns about unfavorable cost impact are being re-evaluated in the light of present monetary values and enormous awards. Other components of a compensation system include the measurement of damages, the form or amount of compensation, the source of compensation funds, case-disposition mechanisms, fund collection and disbursement, and methods of dispute resolution. Three apparently successful injury compensation systems, the New Zealand Accident Compensation Act,24-27 the Swedish Patient Injury Insurance Plan,28-30 and the Workers' Compensation System in the United States,6,31 are available models for analysis and comparison.

New Zealand, since 1974, has defined personal injury by accident to include "medical, surgical, dental, or first aid misadventure." The program merges workers' compensation and automobile protection, and adds coverage for victims of other accidents. Common law actions for negligence are precluded to the extent that an injury is compensable under the no fault system, but it is not yet clear which cases will be compensated and which will be litigated. Financing is by levies on employers and self employed persons, levies on owners and drivers of motor vehicles, and money appropriated by parliament.

Benefits include medical care, transportation to the physician or hospital, funeral expenses, awards for permanent loss or impairment of function, payment for lost earnings, and limited awards for disfigurement or pain and suffering. In exchange for the new program, the injured person has traded the dubious advantage of litigation of torts for a quick and informal administrative procedure. He has traded the possibility of a large award for a more certain, modest payment for injuries, limited pain and suffering, and assurances of income maintenance.

After four years of operation, this innovative program appeared to be working well. Claims were processed rapidly and routinely, and with an acceptable administrative cost. Few claims were appealed beyond the initial level and most were paid without attorney involvement. One of the major difficulties was ascertaining the range of coverage intended by the statutory words.

Sweden, in 1975, established a patient insurance program after general realization that few medical malpractice claims resulted in compensation for the patient. The primary goal was to create a provider-financed scheme for compensating victims of significant medical injuries in three categories: (1) an injury that occurred as a direct consequences of examination, medication, and treatment, and that was not associated with known risks, but excluding injuries or illnesses likely to have arisen irrespective of care rendered; (2) an injury that occurred as a result of incorrect diagnosis or an incorrect interpretation of symptoms, that is, procedures not reflecting generally accepted medical practice; and (3) an injury that occurred as a result of a sudden external event within the health care institution or during transportation by ambulance.

Negligence was discarded as a standard of payment, and the mechanism for discipline of providers was separated from the compensation program. Insurance coverage to pay claimants is purchased from a pool of private carriers by private and government-employed health care providers. Claims are submitted to an insurance office, and most are then paid directly. Appeals are possible to a claims panel, and thereafter may be submitted to arbitration. The patient initially retains the right to proceed in the court system, or may file a complaint with the National Board of Health and Welfare.

Objectives of the program were to overcome some of the disadvantages in the prior fault based system, and to accomplish speedy resolution of claims without the adversary process and litigation. Results of the program do not indicate generation of unduly large numbers of claims, and do not indicate extensive investigation of claims or contests in the level of awards. Review of the program's development will establish the extent of these results, as well as the effects of separating the compensatory side of medical malpractice from the disciplinary aspects.

Workers' Compensation, the oldest branch of modern social insurance, became part of the European legal system long before its acceptance in the United States. Beginning in Germany with the enactment of an Employer's Liability Law in 1871, a number of other continental powers adopted industrial accident insurance acts before the turn of the century. England followed with the Employer's Liability Act of 1880. In the United States, in 1909, Montana enacted a state compensation system for the coal mining industry. Subsequently in 1911, the largest number of state statutes were enacted, and in 1917 constitutional barriers were removed when the Federal Supreme Court upheld the three existing types of compensation laws. The adoption of a compensation act by Mississippi in 1948 made the system universal.

Thus, in a span of approximately 80 years, the inadequacies of the tort system were gradually corrected so that the victims of industrial accidents and their families were adequately and promptly protected. New legal principles were needed, but legislators were slow to grasp this necessity. These new principles established that the great bulk of work accidents should be regarded as part of the unavoidable loss of modern industrial operations, and should not be approached with concepts of fault. The accident toll presently in American industry is nearly 43 million working days annually; at least 16,500 deaths occur each year through routine industrial operations; and accidental limitation of earning capacity involves more than 2 million other workers. Compensation is payable according to a definite scheme. Payment is secured by employers through private insurance, state funds, or self-insurance. Fault has been eliminated. The compensation represents a compromise in which each party surrenders certain advantages in order to gain other more important to him/her and to society. Employers give up the immunity they would enjoy in cases where they are not at fault, and employees accept a smaller, but certain and prompt compensation.

This system appears to have resolved the problems of industrial accident compensation, and no serious argument has appeared for return to the tort system. should it not be asked why the same scheme is not equally appropriate for many other injuries presently administered under the traditional fault system of tort law?³¹

Conclusions

Tort law approaches to the medical malpractice problem have not resulted in a permanent solution due to the inherent disadvantages of the fault approach. In health care, profoundly negative effects involve both delivery and cost. In law, proplaintiff changes have further extended tort law application into the realm of strict liability, and segments of the legal system have effectively opposed most legislative reforms. In government, legislation to date has provided only short-term relief, has been accompanied by disciplinary measures for providers, and has principally resulted in availability of insurance to pay the ever increasing awards and settlements.

For the patient, high quality health care has been accepted as an individual right in modern society, accompanied by the growing awareness that such care includes inherent risks of personal injury related to the health care process, rather than to the underlying illness. For society, the concept of the health care injury, strikingly similar to the industrial accident, appears increasingly attractive as a long-term solution of this complex problem, awarding compensation based on no fault principles.

Many parallels exist in the evolution of the malpractice problem and in the development of workers' compensation systems, as well as in the development of present no fault compensation programs for health care injuries in New Zealand and in Sweden. The ultimate solution is thus on the horizon, as the replacement of our venerable fault and tort law structure by an innovative no fault compensation system.

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Nueva Recomendación en el Tratamiento de Infecciones Genitales Causada por Neisseria Gonorrhoeae en Puerto Rico

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El Centro Latinoamericano de Enfermedades de Transmisión Sexual, afiliado al Departamento de Salud y al Recinto de Ciencias Médicas-U.P.R., lleva a cabo un programa de investigación de resistencia bacteriana a antibióticos de las cepas aisladas de pacientes con gonorrea en Puerto Rico y como correlacionan los resultados in vitro con la efectividad de tratamiento. El 28% de las cepas de Neisseria gonorrhoeae son resistentes a penicilina, por presencia de plásmido o codificada por el ADN cromosómico, y estas causaron una tasa de falla de tratamiento de 24% con este antibiótico. Además se ha determinado que en los pacientes con gonorrea coexiste Chlamidia trachomatis en por los menos 17% de los casos. Se recomienda el uso de terapia doble: espectinomicina por su efectividad y bajo costo para gonorrea y una tetraciclina o eritromicina para C. trachomatis.

esde el año 1943, la penicilina ha sido usada para el tratamiento de infecciones genitales no complicadas causadas por Neisseria gonorrhoeae. La concentración mínima inhibitoria de penicilina requerida par evitar el crecimiento in vitro del 90% (CMI 90) de las cepas de Neisseria gonorrhoeae era entonces de 0.02 ug/ml de penicilina y se administraba una dosis de tratamiento de 150,000 unidades para una tasa de cura mayor de 95\%.\frac{1}{2} Actualmente, para lograr una tasa de cura equivalente en los Estados Unidos, los Centers for Disease Control, (CDC) han recomendado² el uso de 4.8 millones de unidades de penicilina G procainada acuosa (APPG) con probenecid debido a que la CMI 90 para las cepas de Neisseria gonorrhoeae es de 1.0 ug/ml. Esta información refleja la presión selectiva que ha ejercido la penicilina dando paso así a dos tipos de eventos evolutivos en Neisseria gonorrhoeae: mutaciones en el ácido deo xiribonucléico (ADN) cromosomal de la bacteria que posiblemente causan cambios a nivel de la pared celular bacteriana y la adquisición de plásmidos (moléculas de ADN independientes de ácido deoxiribo nucléico cromosómico) que determinan la producción de la

enzima penicilinasa capaz de inactivar la penicilina. Ambos mecanismos aumentan la resistencia bacteriana a penicilina y causan fallas en el tratamiento con las dosis recomendadas actualmente.

El Centro Latinoamericano de Enfermedades de Transmisión Sexual (CLETS) afiliado al Recinto de Ciencias Médicas y al Departamento de Salud, lleva a cabo un programa de investigación del desarrollo de resistencia a antibióticos de las cepas aisladas de pacientes en Puerto Rico y que se correlaciona con la efectividad del tratamiento.

Como resultado de este programa de detección de resistencia bacteriana el CLETS identificó el primer brote causado por cepas de *Neisseria gonorrhoeae* productoras de penicilinasa (PPNG) en el año 1982. Desde ese año hasta el 1984, la prevalencia de estas cepas en Puerto Rico ha sido respectivamente de 1.0, 1.7 y 8.6%. Las cepas de *Neisseria gonorrhoeae* cuya resistencia a la penicilina está determinada por el ADN cromosomico (chromosomally mediated resistant *Neisseria gonorrhoeae* (CMRNG) se han observado en Puerto Rico desde el 1981 con una prevalencia sostenida de un 20%. A diferencia de la situación en Puerto Rico, los C.D.C. no identifican brotes de estas cepas en los Estados Unidos hasta el 1983. La prevalencia de estas cepas en los E.U. en estos momentos es menor del 5%.

En estudios realizados en CLETS se ha observado un 35.7% de fallas en el tratamiento de penicilina con cepas PPNG y un 20% con cepas CMRNG. Esto combinado resulta en un 24% de fallas totales en el tratamiento de los pacientes. Las alternativas para el tratamiento de infecciones causadas por Neisseria gonorrhoea como la serían tetraciclina y eritromicina no son recomendables. Esto se debe a que la CMI 90 de estos dos antibióticos para las cepas de Neisseria gonorrhoeae aisladas en Puerto Rico es respectivamente de 4 y 2 ug/ml.⁴ Con esto se esperaría una tasa de fallas en tratamiento alta. Nuestros estudios han determinado que el antibiótico espectinomicina tiene una tasa de cura alta asociada a una CMI 90 baja. Por lo tanto, el CLETS recomienda para el tratamiento de la gonorrea el uso del antibiótico espectinomicina (Ver Tabla I) por su efectividad y bajo costo. Además, de la espectinomicina, los antibióticos cefotaxima² son efectivos aunque son de costo más alto.

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Tabla I

Terapia Doble para el Tratamiento de Cervicitis o Uretritis				
Gonococcicas - No Complicadas*				

Microorganismos etiológicos de la uretritis o cervicitis	Recomendaciones para Terapia Doble
Neisseria gonorrhoeae	Espectinomicina (Trobicin) a 2 g, I.M.
Chlamydia trachomatis	Tetraciclina 500 mg p.o. 4 veces al día x 7 días
	o
	Doxiciclina 100 mg p.o. 4 veces al día x 7 días
	o
	Eritromicina b 500 mg p.o. 4 veces al día x 7 días

^{*}NOTA: Tomado de las recomendaciones del C.D.C. (Ver. Ref. 2)

Otro de los factores que hay que tomar en consideración en el tratamiento de uretritis y cervicits gonocóccicas, es la frecuente coexistencia de otras infecciones como son las causadas por *Chlamydia trachomatis* y los micoplasmas como *Ureaplasma urealyticum y Mycoplasma hominis*.⁵

De estos microorganismos, Chlamydia trachomatis coexiste con Neisseria gonorrhoeae en no menos de un 17% de los casos. Además, esta bacteria ha sido aislada en Puerto Rico de un 30 a un 50% de los casos, dependiendo del grupo poblacional estudiado. Esto implica que al tratar una infección gonocóccica en un paciente con una terapia única para gonorrea, (por ejemplo, espectinomicina o penicilina acuosa procainada), se podría fallar en el tratamiento de un 17 a 50% de los casos. Chlamydia trachomatis al igual que la Neisseria gonorrhoeae, es un patógeno que puede ocasionar serios daños al sistema reproductivo de la mujer tales como: salpingitis y enfermedad pélvica inflamatoria (PID). Chlamyda trachomatis también puede transmitirse a los recién nacidos ocasionando una pulmonía severa y/o conjuntivitis.

Por estas razones, en estos momentos la recomendación del CLETS para el tratamiento de una uretritis o cervicitis gonocóccica, es que se use una doble terapia que cubra a *Neisseria gonorrhoeae* incluyendo las cepas de CMRNG y PPNG, y además a *Chlamydia trachomatis*. (Tabla I) Una ventaja adicional de esta doble terapia es que corrige la falla de la espectinomicina de no curar la sífilis en el período de incubación, ya que tanto la tetraciclina como la minociclina al igual que la eritromicina (a las dosis recomendadas) abortan la sífilis durante el período de incubación.² Deseamos dejar establecido que la tetraciclina está contraindicada durante el embarazo y en su lugar se debe emplear la eritromicina.²

Summary: The Latinamerican Center for Sexually Transmitted Diseases, an institution under the Health Department and the Medical Sciences Campus- U.P.R., has a research program to study the development of bacterial reistance in isolates of patients with gonorrhea and the correlation of in vitro results with effective therapy. About 28% of Neisseria gonorrhoeae isolates are resistant to penicillin, either codified by a plasmid or by the bacterial DNA, and these strains caused a treatment failure of 24%. Furthermore, in 17% of the patients with gonococcal infections, Chlamydia trachomatis also coexist. It is recommeded at present to use double therapy: spectinomycin for gonorrhea because of the effectiness and low cost, and tetracycline or erythromycin for C. trachomatis.

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a En infecciones orales se recomienda 9 tabletas diarias de trimetoprima/sulfametoxazol (80mg/400mg) por 5 días.

b Se recomienda en mujeres embarazadas. En mujeres que no toleren este régimen se debe administrar 250mg por boca, 4 veces al día x 14 días. Para conjuntivitis en recién nacidos se debe administrar 50mg/Kg/ hora en 4 dosis por 2 semanas. En casos de pulmonía infantil este tratamiento se debe extender a 3 semanas.

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DIAGNOSTICO ANGIOCARDIOGRAFICO



Rafael Villavicencio, M.D., F.A.C.C. Angel F. Espinosa-López, M.D.

In niño de 4 años de edad se hospitaliza por cianosis progresiva y disnea de esfuerzo. Al examen físico se aprecia cianosis moderada de piel y mucosas y en los dedos de las manos puede observarse una configuración parecida a los "palillos de tambor". Se palpa un frémito sistólico a lo largo del reborde esternal izquierdo. Hay un soplo sistólico-eyectivo, rudo grado 4/6 en los espacios intercostales izquierdo 2 y 3. Hay otro soplo pansistólico, regurgitante, grado 2/6 en la región apico-esternal. El S₁ es normal, el S₂ está sencillo. No hay visceromegalia y los pulsos periféricos son normales.

El electrocardiograma (ECG) demuestra hipertrofia ventricular derecha con patrón de sobrecarga sistólica y el eje eléctrico de QRS está desviado a la derecha (+110°). La radiografía de tórax no demuestra cardiomegalia, la "punta" del corazón tiene una configuración redondeada y levantada. Hay concavidad del segmento pulmonar y la vascularidad pulmonar está disminuida.

Se le hizo cateterismo cardíaco con angiocardiografía izquierda y derecha. El ventriculograma derecho en posición anteroposterior y lateral se ilustra a continuación.

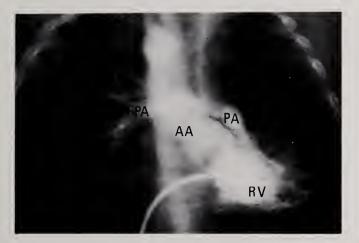


Figura 1. Ventriculograma derecho en posición AP. RV-ventrículo derecho; PA-arteria pulmonar AA-aorta ascendente.

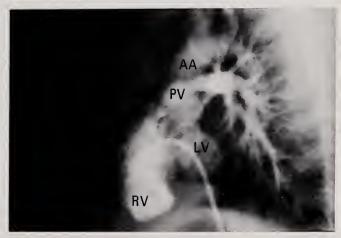


Figura 2. Ventriculograma derecho, posición lateral. RV-ventriculo derecho; LV-ventriculo izquierdo; PV-válvula pulmonar, AA-aorta ascendente.

¿CUAL ES SU DIAGNOSTICO?

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Tetralogía de Fallot

La tetralogía de Fallot (T/F) es una cardiopatía congénita cianosante que se caracteriza por: una comunicación interventricular, estenosis pulmonar infundibular, dextroposición con "acabalgamiento" de la aorta e hipertrofia ventricular derecha.

Van Praagh y colaboradores¹ sugirieron que el defecto principal en la T/F lo constituye un infundibulo subpulmonar anormalmente pequeño que ha sufrido una rotación en sentido anterior, superior y levemente hacia la izquierda. Se ha comprobado y se acepta generalmente que en la T/F clásica el septo infundibular demuestra esta desviación típica. Como resultado tenemos un mal alineamiento entre el septo infundibular y el trabecular produciéndose la típica estenosis infundibular y el defecto interventricular.

La válvula pulmonar en la T/F puede ser normal, pero en ocasiones es bicúspide y estenótica con un anillo valvular pequeño y obstructivo.² Pueden coexistir en la T/F anomalias de las arterias pulmonares como estenosis focales o diseminadas asi como hipoplasia, ausencia congénita y origen anómalo de alguna de ellas.

Las arterias coronarias en la T/F han sido objeto de discusión, particularmente en la última década. A pesar de que el origen y distribución epicárdica de las arterias coronarias pueden demostrar todas las variaciones que se observan en corazones normales, hay una anomalía coronaria en la T/F que debe reconocer en el angiograma pre-operatorio. Esta anomalía es el origen de la arteria coronaria descendente anterior de la arteria coronaria derecha.³ Cuando esto ocurre, la arteria coronaria descendente anterior en su trayecto descendente cruza el área del infundíbulo derecho antes de llegar al surco interventricular anterior. El conocimiento de este trayecto coronario através del infundibulo es de vital importancia para el cirujano en el momento de la corrección quirúrgica de la T/F. Este acto operatorio conlleva muchas veces una resección amplia del área infundibular para poder resolver de forma efectiva el problema obstructivo del lado derecho que conlleva esta cardiopatía. La incidencia de esta anomalía coronaria se ha descrito desde un 2 a un 5% en las T/F.4

El arco aórtico también sufre variaciones en la T/F; se conoce la existencia de un arco aórtico derecho en cerca de un 30% de las tetralogías. Muy raras veces puede verse un arco aórtico doble en esta cardiopatía cianosante.

Otras anomalias asociadas con la T/F incluyen: defecto interatrial del tipo secundum (Pentalogía de Fallot); canal atrioventricular (más frecuente en pacientes con el síndrome de Down); anomalias del retorno venoso; anomalía de Ebstein de la válvula tricuspídea y con menor frecuencia lesiones del lado izquierdo como estenosis y malposición de la válvula mitral; estenosis aórtica subvalvular, etc.

El diagnóstico de T/F debe diferenciarse de otras cardiopatías congénitas, principalmente aquellas en que tengamos cianosis, hipovolemia pulmonar e hipertrofia ventricular derecha. Algunas pueden ser excluidas por el examen físico, el electrocardiograma y la radiografía de torax, como sucede con la atresia tricuspidea, la anomalía

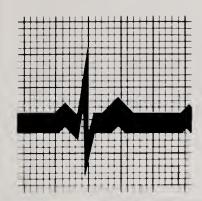
de Ebstein de la válvula tricuspídea y el síndrome de Eisenmenger. La diferenciación es algo más dificil en la transposición de los grandes vasos con defecto interventricular y estenosis pulmonar. En este caso el ecocardiograma es particularmente útil y el diagnóstico se confirma casi siempre por angiocardiografía. El tronco arterioso con hipoplasia de las arterias pulmonares puede ser en ocasiones dificil de distinguir de la forma severa de T/F, aún con la angiocardiografía.

El diagnóstico angiocardiográfico de la T/F se obtiene mediante la inyección de material de contraste en el ventrículo derecho. En la figura 1 puede observarse la trabeculación marcada del ventrículo derecho hipertrófico, la obstrucción infundibular con la formación de una cámara en el tracto de salida derecho y un anillo valvular pequeño con estenosis pulmonar valvular. Puede apreciarse también una arteria pulmonar pequeña, una aorta grande (tres veces al tamaño de la pulmonar) y un arco aórtico derecho. En la figura 2, se ve la relación de los grandes vasos, con una arteria pulmonar anterior e hipoplásica y la válvula pulmonar estenótica. Puede apreciarse como se opacifica el ventrículo izquierdo de el derecho por un corto circuito de derecha a izquierda a través del defecto interventricular.

El tratamiento de la T/F es quirúrgico, con el fin de intentar proveer una calidad de vida óptima a corto y a largo plazo con una mortalidad y morbilidad mínima. Se reconoce que mientras más temprano se lleve a cabo la corrección, mejor será el resultado a largo plazo. Sin embargo, existen situaciones en que estos infantes con T/F requieren procedimientos quirúrgicos paliativos antes de intentar la corrección total.

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ELECTROCARDIOGRAM OF THE MONTH

Charles D. Johnson, M.D., FACC

Figures 1 and 2 are those of a 11-year-old acyanotic female with a history of fainting spells and a heart murmur. As an adult, there are a peculiar personality and behavior, a right ventricular (RV) lift, an increase in the heart rate on standing and a narrow subxiphoid rib cage angle. An M-mode echocardiogram revealed abnormal septal motion. A chest roentgenogram showed decreased pulmonary vascularity, hypoplastic right pulmonary artery (PA) and enlargement of the left PA with convex bulging (post-stenotic dilatation).

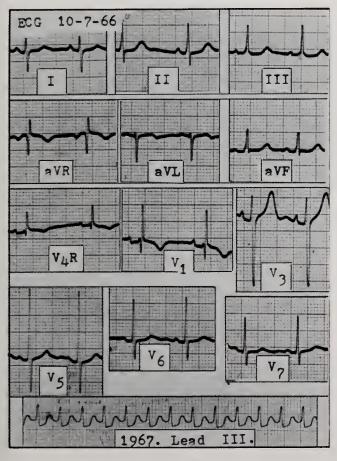


Figure 1.

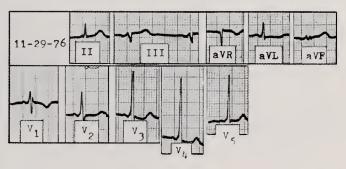


Figure 2.

Questions

- 1. What are the ECG diagnoses?
- 2. What are possible clinical diagnosis?

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Answers

"Trilogy of Fallot" - valvular pulmonic stenosis (PS); 80 mm Hg gradient; PA pressure 19/10 mm Hg.

Atrial septal defect (ASD)- 1 x 2 cm. No systemic oxygen desaturation.

Surgical closure of ASD and open pulmonary valvular commissurotomy.

"SVT" - near 300 bpm.

During her first pregnancy, she suffered chest pain, dyspnea, palpitations and was blue. There was a difficult delivery. During the second pregnancy the cardiac arrhythmias, including ventricular premature beats, improved markedly.

Wolff-Parkinson-White (WPW) syndrome. Some electrocardiograms (ECG) suggested a delta wave, which has grown larger and more obvious in recent years.

"PAT" at age 19 years. Her symptoms continued.

Therapy has consisted of quinidine and propranolol.

Figure 1 was obtained at 11 years of age prior to cadiac surgery. There are: peaked P waves suggesting right atrial enlargement, a QRS width of 0.08 S, right axis deviation (RAD o $105^{\circ}-110^{\circ}$), right ventricular hypertrophy (RVH)- rsK and inverted T waves in V_4R and V_1 - and an initial notch of the QRS complex in lead III and aVF. The lead III strip on the bottom shows supraventricular reentry tachycardia (probably bypass).

Figure 2, age 21 years, shows preexicitation conduction, with delta waves in many leads; the P-R interval is short.

Comments

The "trilogy of Fallot", first described by Morgagni in 1761, comprises valvular PS, and ASD or patent foramen ovale with a right to-left shunt and an intact ventricular septum.

The typical ECG of the trilogy of Fallot is variable depending on the relative severity of the PS and size of the atrial communication. It may manifest:

P congenitale - tall and peaked P waves in leads II and

Marked RAD of the QRS forces- +60- $+210^{\circ}$ (+120 $^{\circ}$ -150 $^{\circ}$).

RVH in all cases; systemic pressure overload; tall predominant R waves in several precordial leads, $V_{1^{-4}}$, leads II, III and aVF; slurred R wave in V_{1} . Occasionally, complete right bundle branch block. The QRS vector is oriented anteriorly, rightward, inferiorly or superiorly (Type A RVH). The septal vector is anterior, or anterior and leftward.

Left axis deviation is rare.

The ST segment is displaced with upward convexity. The T waves are pointed negative, of primary ischemic

type.

The WPW syndrome has been observed in trilogy of Fallot, as well as in isolated PS or ASD. It makes the diagnosis of ventricular hyperthorpy inaccurate in congenital heart disease, and favors reentrant arrhythmias. A "SVT" in the older child makes manifest or concealed WPW syndrome likely.

Usually, P congenitale and RVH in the trilogy of Fallot are of greater severity than in tetralogy of Fallot; however, this patients ECG appears to be an exception.

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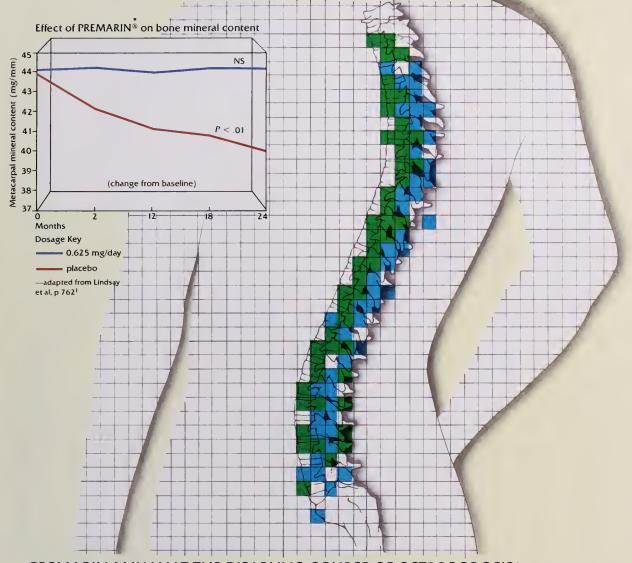
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POSTMENOPAUSAL BONE LOSS THAT INCAPACITATES



PREMARIN MAY HALT THE DISABLING COURSE OF OSTEOPOROSIS*

Osteoporosis has an enormous epidemiological impact: it affects 10 million American women, and 26% of all women over age 60.2 The disease begins silently and progresses inexorably for 15 to 20 years, until disabling complications occur.3

To minimize osteoporotic damage, the condition must be detected early and treated promptly. For many patients, PREMARIN is optimal therapy for osteoporosis, as part of a comprehensive program that includes exercise, good nutrition, and calcium supplements. In a controlled study of postmenopausal and oophorectomized women, PREMARIN (Conjugated Estrogens Tablets, U.S.P.) doses of 0.625 mg/day prevented loss of metacarpal mineral content (see graph above).

PREMARIN® (CONJUGATED ESTROGENS TABLETS, U.S.P.)

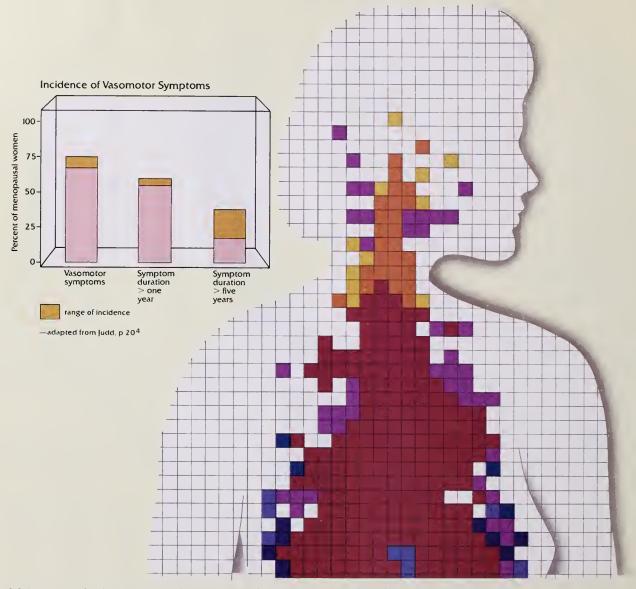


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*Conjugated Estrogens Tablets have been evaluated as probably effective for estrogen-deficiency-induced osteoporosis.

Please see last page for brief summary of full prescribing information.

VASOMOTOR SYMPTOMS THAT DEMAND INTERVENTION

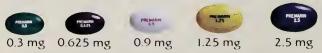


PREMARIN RELIEVES MODERATE TO SEVERE VASOMOTOR SYMPTOMS

Vasomotor symptoms are the most common manifestation of the menopause, affecting up to 75% of menopausal women. Of these, 80% may suffer for more than a year and up to 50% for more than five years. These symptoms can disrupt a woman's life by chronically interrupting sleep, resulting in anxiety and irritability.

In a study of postmenopausal women suffering severe episodes of cutaneous flushing, symptoms improved markedly after administration of estrogen⁵—the treatment of choice for moderate to severe vasomotor symptoms. The estrogen of choice is PREMARIN, the most widely prescribed estrogen for over 40 years. PREMARIN (Conjugated Estrogens Tablets, U.S.P.) relieves moderate to severe vasomotor symptoms of the natural menopause, as well as the acute and often severe symptoms of surgical menopause.

PREMARIN® (CONJUGATED ESTROGENS TABLETS, U.S.P.)



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VAGINAL ATROPHY THAT



PREMARIN RESTORES THE VAGINAL ENVIRONMENT

In the postmenopausal woman, decreasing levels of estrogen can have devastating effects on a woman's sexual functioning. The pH of vaginal secretions rises, promoting the growth of contaminating organisms. The vaginal epithelium dries and thins, becoming susceptible to irritation, injury, and infection. Sexual relations may be difficult or impossible.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream focuses therapy at the site of the problem. Vaginal dryness is relieved, pH reverts to its normal acidity, and the epithelium thickens and becomes more resistant to injury and infection. With the vaginal environment returned to its premenopausal state, sexual function may improve.

PREMARIN® (CONJUGATED ESTROGENS, U.S.P.) Vaginal Cream



BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE

PREMARIN* Brand of Conjugated Estrogens Tablets, U.S.P.
PREMARIN* Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies and truther supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer. snarpy since 1909 in eight officered tareas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose in view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible symptoms should be utilized and medication should be discontinued as soon as possible When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic

ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α -dihydroequilin, together with smaller amounts of 17α -estradiol, equilenin, and 17α -dihydroequilenin as salts of their sulfate

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1 Moderate to severe vasomotor symptoms associated with the menopause (There

is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

- Atrophic vaginitis
- Kraurosis vulvae Female hypogonadism

- Female castration
 Primary ovarian failure
 Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease
- metastatic disease

 B Prostatic carcinoma palliative therapy of advanced disease

 9 Postpartum breast engorgement Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large does in festingens.

large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING
PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P) Vaginal Cream is indicated in the treatment of atrophic vaginits and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BEFFECTIVE FOR ANY PURPOSE DURINIG PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following

conditions. 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen-dependent neoplasia 3. Known or suspected pregnancy (See Boxed Warning). 4 Undiagnosed abnormal genital bleeding. 5 Active thrombophielbits or thrombophielbits or thrombophielbits or thrombophielbits, thrombosis, or thrombophielbits or statement of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain

thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increases the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancier of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2 to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. It feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estroge

pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk. Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in

tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic struulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. or renal dystunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastiquia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency metabolic bone diseases associated with hypercalcemia or in young patients in whom insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete. The following changes may be expected with larger doses of estrogen:

a Increased sultobromophthalein retention b Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased orepinephrine-induced platelet aggregability c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.

- d Impaired glucose tolerance
 e Decreased pregnanediol excretion.
 f Reduced response to metyrapone test

Reduced response to metyrapone test g Reduced response to metyrapone test g Reduced serum folate concentration.

In Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives. breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion (cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hari, insultism; steepening of corneal curvature; intolerance to contact lenses, headache, migrane, dizziness, mental depression, chorea; increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, changes in libido ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females DOSAGE AND ADMINISTRATION:

PREMARIN* Brand of Conjugated Estrogens Tablets, U.S.P.

DOSAGE AND ADMINISTRATION:
PREMARIN* Brand of Conjugated Estrogens Tablets, U.S.P.

1 Given cyclically for short-term use only. For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 125 mg or more daily). The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals 2. Given cyclically. Female hypogonadism. Female castration. Primary ovarian tailure. Osteoporo-

Female hypogonadism — 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration if bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium. If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic rigimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 75 mg daily in divided doses for 20 days. During the last five days of estrogen therapy, give an oral progestin. It bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

beloeding Female castration and primary ovarian failure—125 mg daily, cyclically Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

will provide effective control.

Osteoporosis (to retard progression) — 1.25 mg daily, cyclically.

3 Given for a few days. Prevention of postpartum breast engorgement — 3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4 Given Chronically. Inoperable progressing prostatic cancer — 1.25 to 2.5 mg three times daily. Inoperable progressing breast cancer in appropriately selected men and postmenopausal women.— 10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate progressing breast cancer in the experience of the control of the progressing breast days and appropriate progressing breast days and appropriate progressing breast days are progressed by the progressing breast days are progressed.

measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal

PREMARIN* Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae

The lowest dose that will control symptoms should be chosen and medication should be

discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off)

Attempts to discontinue or taper medication should be made at three to six month intervals

Usual dosage range 2 to 4 g daily, intravaginally or topically, depending on the severity of the

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

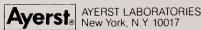
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References: 1. Lindsay R. Hart DM, Clark DM. The minimum effective dose of estrogen for prevention of postmenopausal bone loss Obstet Gynecol 1984.63.759-763. 2. Katz WA Rheumatic Diseases. Diagnosis and Management Philadelphia, JB Lippincott Co. 1977, p. 672. 3. Reese WD. A better way to screen for osteoporosis Contemp Ob/Gyn. 1983, 22(November). 116-131.4. Judd HL. After the menopause. Transition. 1983, 1. 19-30. 5. Erlik Y. Tataryn IV, Meldrum DR, et al. Association of waking episodes with menopausal hot flushes. JAMA. 1981. 245. 1741-1744. 6. Meldrum DR. The pathophysiology of postmenopausal symptoms. Sem Reprod Endocrinol. 1983, 1 (February). 11-17.





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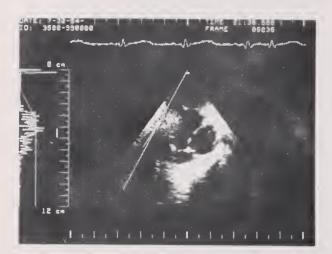
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ECHOCARDIOGRAPHY CASES

Charles D. Johnson, M.D., F.A.C.C.

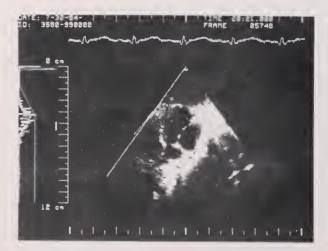
A lthough applied initially in the evolution of echocardiography, M-mode echocardiography has provided only indirect nonspecific data in atrial septal defects (ASD). More recently two-dimensional and Doppler echocardiography have assumed a direct role in the diagnosis, localization and determination of hemodynamics in the various types of ASDs, as demonstrated in the following patient and review.



Case History

This one year old male had a grade 2 systolic ejection murmur at the upper left sternal border; the components of the second heart sound were split without respiratory variation.

He was studied using the Honeywell two-dimensional and Doppler echocardiograph (Biosound, Indianapolis, Ind).



Figures 1 and 2. Are suhcostal two-dimensional freeze-frame views of the atria and interatrial septum (AS). Time markers are at the top and bottom margins of the frame (hetween the heavy lines is 1 second-S). An electrocardiogram is above the image. An A-mode trace with a ramp and gain, and a depth calibration scale are located on the left side. There is a mid-septal secundum defect with a T artifact (dense hright echoes at the margins of the defect). There appears to he a second defect in the high AS-a sinus venosus defect. In Figure 2, there is possibly a third lower or septal defect, or signal dropout. The right atrium (RA) appears enlarged.

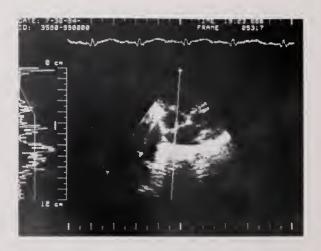
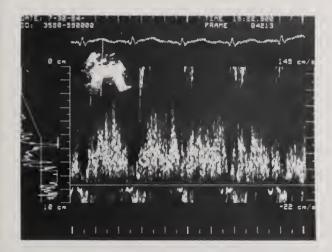
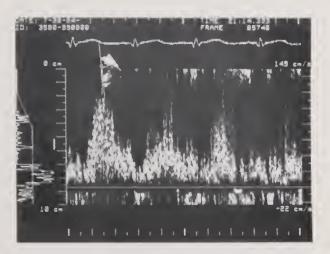


Figure 3. Two-dimensional echocardiographic freeze-frame. Subcostal long-axis view at a different angulation than in Figures 1 and 2. The cursor with the sample volume (SV) is placed perpendicularly on the right atrial side and within a central, secundum ASD, parallel to ASD flow, at a SV depth of $5-5\ 1/2\ cm$.

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Figures 4 and 5. Subcostal 4-chamber views of the AS with the SV placed over the right side of the secundum defect parallel to flow (left upper insert). Pulsed-wave Doppler (PWD). There is a flow velocity calibration scale on the right side of the still-frame (10 cm/S between each calibration step). Still-frame prints of Doppler transatrial septal velocities (TASV) are shown. The Doppler flow tracings illustrate positive (toward the transducer) continuous (less at end-diastole) systolic and diastolic



turbulent, rough flow. The peak TASV is 1.3 M/S, and the mean flow velocity is 53 cm/S. This reflects a left-to-right shunt (Qp/Qs) of 2.5:1, applying the TASV (cm/S)-Doppler flow (Qp/Qs) graph developed by Marx el al. Mean TASV and other flows were computed by digitizing the area under the time velocity curve during systole and diastole, using an Apple II Plus computer (Cupertino, CA) and a dedicated software disk program (Biodata. Davis, CA).

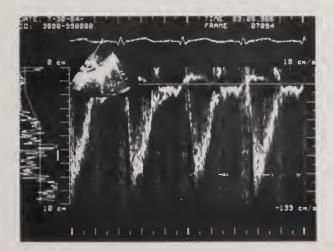


Figure 6. Is a freeze-frame (left upper insert) PWD flow trace with the SV placed in the main pulmonary artery (MPA) from the parasternal short-axis view. There is a negative (flow away from the scanhead) systolic flow below the zero baseline representing pulmonary forward flow. There is a presystolic "a" wave negative flow. Peak flow velocity (V) = 1.4 M/S.

Calculated PA flow (as above) was 9744 cc/M² (Qp), and aortic (Ao) flow 4795 cc/M² (Qs), for a Qp/Qs ratio of 2:1.

Discussion

Echocardiography in secundum ASD may demonstrate:

M-Mode

- 1. Right ventricular (RV) dilatation as volume overload 1.4 cm/M² supine and 1.7 cm/M² with the patient in the left lateral position; this is increased in about 98% of patients. There is also RA enlargement.
- 2. Paradoxical (type A) or flat (B), or normal motion of the ventricular septum (VS). VS motion is abnormal in about 87% of cases. There is gradual and continuous anterior systolic motion, which may be dyskinetic from the subcostal view. Both sides of the septum should be analyzed.
- 3. In the presence of pulmonary hypertension (PH), there may be paradoxical sudden anterior septal movement in early systole with subsequent motion away from the chest wall during systole.
- 4. Increased amplitude of opening excursion and the E-F slope of the tricuspid valve (TV) relative to the mitral valve (MV), and increased leaflet separation during diastole (due to the augmented trans TV (flow) may occur. Diastolic fluttering of the TV (turbulence secondary to the high shunt flow) can also occur.
- 5. Pseudo-systolic anterior motion and decreased D-E and E-F slopes of the MV may be present.
- 6. The left atrium, left ventricle (LV) and aortic root are normal.
- 7. The right PA is enlarged on the suprasternal notch (SSN) view.
- 8. Following surgical closure septal motion and RV dilatation may or may not normalize. In one study abnormal septal motion persisted in 68% and RV dilatation in 77%.
- 9. M-mode echocardiography is indirect and not sufficiently sensitive or specific; but only rarely is it normal if the shunt approaches 2:1 in ratio. A normal M-mode study with normal RV dimension and septal motion is reliable evidence against a surgically significant shunt, but the echocardiogram may be normal if the shunt is less than 1.5:1. If the VS diastolic motion is 5 mm, the shunt is large, and compares with the Qp/Qs ratio.

Two-Dimensional Echocardiogram

- 1. Direct visualization of the defect and its anatomical types. There are thinning and deficient septum primum over the central, fossa ovalis region of the septum. There are remnants of the atrial septum on both sides of the defect with dense edges (T artifact), which move with constant relation to the Ao root during the cardiac cycle. Normally, there is central thinning of this area of the AS at the level of the foramen ovale, as a straight linear echo.
- 2. The subcostal 4-chamber view is preferred because the beam is more nearly perpendicular to the AS. Direct visualization is feasible in approximately 98% of infants and children and often in adults. The apical 4-chamber and standard parasternal views may result in false echo dropout in the fossa ovalis area,

- because the ultrasound beam is parallel to the AS. The low left parasternal and right parasternal views may also be useful.
- 3. Transoesophageal cross-sectional echocardiography was considered superior to the transthoracic approach as a highly sensitive method for detection and evaluation; it was also used in detection of sinus venosus defects.
- 4. Sinus venosus ASD is a defect located near the orifice of the superior vena cava, and is the most difficult type to detect (55% sensitivity). A subcostal approach is used, applying antero-superior tilt with clockwise rotation from a midsternal septal view.
- 5. Coronary sinus defect can exist in the lower AS.
- 6. Lutembacher's Syndrome manifests RV enlargement (volume overload without PH), abnormal VS motion and the typical pattern of mitral stenosis.
- 7. The VS is flat or indented convexly into the LV during diastole by the enlarging RV, reflecting the relative filling of the two ventricles; rapid anterior VS displacemant occurs with the onset of systole. The posteriorly displaced VS must be differentiated from an overriding Ao.
- 8. The LV may be distorted, small or normal. It may have clockwise angular rotation or displacement with systole.
- 9. RV and PA dilatation; changes in the motion pattern of the right PA may exist. The RV wall thickness is usually normal.
- 10. Mitral valve prolapse may be present (observed in 10-37% of patients with ASD).
- 11. Post-balloon atrial septostomy (as flail remnants of the torn, flap, septum primum) and surgical septectomy (Blalock-Hanlon - a large, posterior sinus venosus-type defect is common) ASDs may also be visualized.
- 12. Ostium Primum ASD-located low in the interatrial septum contiguous with the atrioventricular valve rings. There may be abnormalities of MV motion, and the MV may be seen in the LV outflow tract, with prolonged MV-septal apposition in diastole; the RA and PA are enlarged. Parasternal long-axis or subcostal views may show abnormal displacement of the MV into the LV outflow tract ("goose-neck"), and an absence of interatrial septal tissue in the region of the VS crest. The superior margin of the defect often casuses a bright linear echo density. On parasternal short-axis views, there is frequently a cleft in the anterior leaflet of the MV. Thin lines of echoes connect the ridge of the cleft to the VS, representing abnormal chordal attachments to the septum. The inferior and superior parts of the cleft separate in diastole and there is superior narrowing of the LV outflow tract.
- 13. Common Atrium by subcostal and apical 4-chamber views no AS echoes are visualized.

Contrast Echocardiography

Contrast studies enhance the accuracy of ASD detection. Peripheral arm vein injection of indocyanine green, saline or the patient's own blood can be used.

- A. Left-to-right shunt a. A small amount of contrast may also move from the RA to the left atrium (LA), especially during a Valsalva or Mueller manuever or during crying, during the rapid filling phase of ventricular diastole and onset of ventricular systole; b. A negative washout/contrast image in the RA (end-systole, early diastole) and inferior vena cava, which is less sensitive. On M-mode or two-dimensional echocardiograms, a presystolic contrast effect occurs in the inferior vena cava. Early after surgical closure of the defect, residual shunting may be evaluated by contrast echocardiography, as well as the detection of true small shunts subsequently.
- B. Right-to-left shunt Contrast moves from the RA to LA and LV through or within the MV; it reaches the LV and RV simultaneously, or the RV before the left heart fills. This is very sensitive and, detecting shunts as small as 3%. If the LA is injected directly, contrast first appears in the LV and later in the RV. Contrast studies can identify communications that may be too small to image even with high resolution real-time scanning. Agents opacifying the LV after intravenous injection are capable of providing direct ultrasound contrast of congenital left-to-right shunts.

Pulsed Doppler With Two-Dimensional Guidance

A subcostal 4-chamber view is the dominant approach, as the beam is perpendicular to the AS and the SV is parallel to shunt flow. 3.5 or 5 MHZ transducer may be used in children.

- 1. The TASV, mean and maximal, of the left-to-right shunt is augmented; mean 40.7, range 22-60 cm/S (normal-mean 15.6, range 5.6-21 cm/S). The SV is placed in the RA over the ASD; the defect itself may be threaded from the LA. The flow is continuous, scattered and rough; the flow profile is toward the transducer (positive on the display) in late systole through diastole with accentuation (second positive deflection) at end-diastole (flow during ventricular diastole, atrial systole and ventricular systole). The area under the time-velocity curve during systole and diastole is digitized. An estimate of the shunt magnitude is possible by conferring with a mean velocity flow-magnitude of shunt graph. Likewise, Doppler pulmonary/systemic (Qp/Qs) flow ratios correlate well with catheterization and fairly well with radioisotope-derived ratios.
- 2. Qp/Qs areas under the flow velocity curves (flow velocity integrals) can predict shunt size. PA or TV flows reflect pulmonary flow, and Ao flow the systemic flow. The RV outflow tract (RVOT) might be used if the PA flow is too highly disturbed to determine velocity.
- 3. Flows measured distal to the TV, pulmonic valve (PV) and aortic valve are quite similar in a given individual. The mitral orifice is difficult to measure and variable values are obtained.
- 4. There is TV (RA outflow tract) frequency dispersion/turbulence in mid and late diastole (due to the augmented trans TV flow and velocity).

- 5. Pulmonary flows may be disturbed (broadened spectral pattern) due to the high velocities. Occasionally, there is systolic turbulence in the RVOT. The Series Effect (extension of the flow disturbance downstream) and Vortex Shed Distance can displace the origin of the flow disturbance into the RV.
- 6. The maximal atrial V is 1-1.3 M/S (Hatle), and is higher if coarctation of the Ao is associated. The velocity is lower if the SV is positioned on the left side of the AS, and it decreases on inspiration. There may be a short period of absent or reversed flow at the beginning of systole or with atrial relaxation. The PV V in ASD may increase 20-30 cm/S; mean 29, peak 100 cm/S (normal mean 20, peak 78 cm/S) and be 2-3 times as high as in the Ao. The Ao and MV velocities diminish. V ratios have been proposed to assess the magnitude of shunt: PA/Ao, TV/MV. TV V may equal or exceed MV V and be sustained throughout diastole. Following closure of the defect the V ratios may normalize.
- 7. The Doppler Index, RSV/LSV (RV and LV stroke volumes), has been proposed to estimate the magnitude of shunt flow-mean ratio of 2.26 in ASD and 0.99 in normal subjects.
- 8. Jugular vein velocity curves have been suggested to quantitate flow, but are of doubtful value. Characteristic findings are an earlier S summit and a deep negative 0, depending on flow.
- 9. Two-dimensional color-coded Doppler imaging and flow mapping are in the initial stages of application in evaluation of shunt flows. Multiple jet profiling may be applicable in the future.
- 10. The ascending Ao can be imaged from the SSN, subcostal and precordial views, and the TV from the apical 4-chamber view; a parasternal shortaxis view with the patient in a high left lateral position provides PA visualization. The flow pattern can be recorded without imaging with PWD.
- Ostium primum ASDs may be identified with Doppler. TV and MV flow disturbances can be observed.
- 12. ASD with PH Time-to-Peak V (TPV) 100 mS; absetn presystolic "a" wave; TPV corrected for RV ejectin time (RVET) correlates with mean PA pressure. The RVOT pulse may show midsystolic notching (normally it is dome-like), and a decreased acceleration (AT) and AT/RVET ratio. With mainly right-to-left shunting flow velocity may be recorded in the opposite direction. Lower velocities are recorded on the right side of the AS, and if severe low velocities occur across all 4 valves, including the TV and PV, and even failure to record shunt flow across the ASD. High velocities of tricuspid regurgitation (TR) and pulmonic regurgitation (PR) with little fall during diastole may be helpful diagnostically.
- 13. Audio signal

Differential Diagnosis

1. RV volume overload on M-mode is nonspecific because it occurs also in TR, PR, anomalous pulmonary venous return, ventricular septal defect,

- Ebstein's anomaly, congestive heart failure, etc.
- 2. TR and PR may be associated with an ASD. The diastolic negative flow disturbance of TR can be located along the RA septal surface but it manifests a systolic flow disturbance in the RA.
- 3. Superior vena cava flow (which has a similar direction and pattern) may be mistaken for ASD flow, particularly sinus venosus defects.
- 4. Sinus venosus defects are difficult to visualize on occasions.
- 5. Coronary sinus septal defects.
- 6. A systolic and diastolic flow signal in the RA near the TV may be observed without augmented flow, due to coronary sinus flow.
- 7. False positive echo dropout using standard precordial and apical 4-chamber views due to parallel beam imaging. Beam width artifact can fill-in an ASD.

Two-dimensional echocardiography visualized 89% of secundum defects and 100% of ostium primum defects, but false negatives still occurred, especially in sinus venosus defects (56% accuracy). Two-dimensional contrast and Doppler improve the results and compliment echocardiography. Combined two-dimensional imaging and Doppler are superior to combined M-mode and Doppler. Doppler alone offers 77-100% sensitivity, specificity and predictive value in ASD.

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THE PUERTO RICO HEART ASSOCIATION ANNOUNCES ITS ANNUAL SCIENTIFIC SESSION

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CERROMAR BEACH HOTEL DORADO, PUERTO RICO SEPTEMBER 13–15, 1985

GUEST SPEAKERS

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JAMES C. BUELL, M.D. PHOENIX, AZ

NORA GOLDSCHLAGER, M.D. SAN FRANCISCO, CA

JOHN MESSENGER, M.D. LONG BEACH, CA

W. DUDLEY JOHNSON, M.D. MILWAUKEE, WI

KARL WEBER, M.D. CHICAGO, IL

NATHANIEL REICHEK, M.D. PHILADELPHIA, PENN

RICHARD WALSH, M.D. SAN ANTONIO, TX

TOPICS OF DISCUSSION

"EXPERIMENTAL HEART TRANSPLANTATION FOR THE NEONATE" "IMMUNOLOGIC EXPERIENCE IN CARDIAC TRANSPLANTATION" "THE PERI-OPERATIVE CARE OF THE INFANT" "SURGERY FOR DIFFUSE CORONARY DISEASE" "STRESS AND CARDIOVASCULAR DISEASE" "MANAGEMENT OF PERSISTENT ACUTE MYOCARDIAL ISCHEMIA" TREATMENT OF ACUTE MYOCARDIAL INFARC-TION: THROMBOLYTICS VS. MECHANICAL RE-PERFUSION" "LEFT VENTRICULAR HYPERTROPHY, PATHOGENESIS AND IMPLICATIONS OF THERA-PY" "ASSESSMENT OF VENTRICULAR FUNCTION" "C.H.F.; PATHOGENESIS, AND TREATMENT WITH THE NEWER INOTROPIC AGENTS" "ELECTRO-PHYSIOLOGY; PACEMAKER PROGRAMMABILITY AND DUAL-CHAMBER PACING"

INFORMATION

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What can you do for hypertensives like Janet M?



Rely on one-tablet-a-day dosage and cardioselectivity.

"Real life" efficacy

Janet M represents 4,533 women age 40 to 55 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Lessens risk of bronchospasm

Propranolol use has been associated with bronchospasm even in patients with no history of wheezing or dyspnea. Unlike propranolol, TENORMIN exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. Although this preference is not absolute, wheezing and shortness of breath seldom occur.

See following page for brief summary of prescribing information.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy!

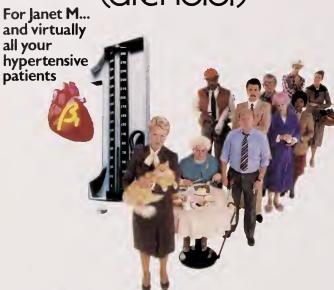


For Janet M...and virtually all your hypertensive patients

TENORMIN® (atendal)







TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension.

DESCRIPTION: TENORMIN\(^1\) (atenoloi), a synthetic, beta₁-selective (cardioselective) adrenoreceptor biocking agent, may be chemically described as benzeneacetamide, 4-[2'-hydroxy-3'-[(1-methyleithyl) amino] propoxy]-. Alenoloi (free base) has a micecular weight of 266 it is a relatively polar hydrophilic compound with a water solubility of 26 5 mg/ml at 37° C and a log partition coefficient (octanol/water) of 0.23 it is freely soluble in 1N HCI (300 mg/ml at 25° C) and less soluble in chloroform (3 mg/ml at 25° C).
INDICATIONS AND USAGE: TENORMIN (atenoloi) is indicated in the management of hyperencial It may be used along or proportiantly with beta antibiopartensive speats, particularly with a

sion. It may be used alone or concomitantly with other antihypertensive agents, particularly with a

It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiact tailure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more sever eliature. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and /or be given a diuretic and the response observed closely. It cardiac failure continues, despite adequate digitalization and diuretic. TENORMIN therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated it withdrawal symptoms occur.

Fronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVED.

drawal symptoms occur
Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN
GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do
not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is
not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated
at 50 mg and a beta;-stimulating agent (bronchodilator) made available. It dosage must be
increased, dividing the dose should be considered in order to achieve lower peak blood

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN betore surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. It treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and frichloroethylene. TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its

"TENORMIN, like other befa blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenoi with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, prolound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V). Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels. Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with
impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg., reseprine) may have an additive effect
when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine
depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine
concurrently, the beta blocker should be discontinued several days before the gradual withdrawal
of clonidine

of clonidine Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies.support this finding. Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both mate and female dogs at all tested dose levels of atenolof (starting at 15 mg/kg/day or 7 5 times the maximum recommended human dose) and increased incidence of afraid degeneration of hearts of male rats at 300 mg but not 150 mg atenolof/kg/day (150 and 75 times the maximum recommended human dose).

respectively)

USAGE IN PREGNANCY: Pregnancy Category C. Atenoiol has been shown to produce a doserelated increase in embryo / tetal resorptions in rats at doses equal to or greater than 50 mg //kg or
25 or more times the maximum recommended human dose. Although similar effects were not seen
in rabbits, the compound was not evaluated in rabbits at doses above 25 mg //kg or 12.5 times the
maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the
potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since
most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving
atenoid.

atencial Pediatric Use: Satety and effectiveness in children have not been established ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patent (U.S. studies) or elicited (eg. by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo—freated patients than when these reactions were volunteered. Where trequency of adverse effects for TENORMIN and placebo is smilar causal relationship is upor quant. is similar, causal relationship is uncertain

The following adverse-reaction data present frequency estimates in terms of percentages first trom the U.S. studies (volunteered side effects) and then from both U.S. and toreign studies (volunteered side effects). d and elicited side effects)

teered and elicited side effects)

U.S. STUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)
CENTRAL NERVOUS SYSTEM / NEUROMUSCULAR dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)
GASTROINTESTINAL diarrhea (2%-0%), nausea (4%-1%)
RESPIRATORY (See WARNINGS) wheeziness (0%-0%), dyspnea (0.6%-1%)

RESPIRATORY (See WARNINGS), wheeziness (0%-0%), dyspnea (0.6%-1%) TOTALS U.S. AND FOREIGN STUDIES: CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/ NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), treaming (3%-1%), latingue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL diarrhea (3%-2%), nausea (3%-1%)
RESPIRATORY (see WARNINGS), wheeziness (3%-3%), dyspnea (6%-4%)
MISCELLANEOUS. There have been reports of skin rashes and for dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered it any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

tored following cessation of therapy

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported
with other beta-adrenergic blocking agents, and may be considered potential adverse effects of
TENORMIN (atenoiol)

HENCHMIN (atenoiol)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress

Central Nervous System: Reversible mental depression progressing to calationia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased per-

place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased per-formance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The occilomucocutaneous syndrome associated with the beta blocker practoiol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practoiol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overon emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia. In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted. Bradycardia: Atropine or another anticholinergic drug. Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker. Congestive Heart Failure: Conventional therapy. Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or nor-epinephrine may be useful in addition to atropine and digitalis. Bronchospasm: Aminophylline, isoproterenol, or atropine. Hypoglycemia: Intravenous glucose.

Bronchospasm: Ammophylline, isoproterenol, or atropine.
Hypoglycemia: Intravenous glucose
DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a
day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within
one to two weeks. If an optimal response is not achieved, the dosage should be increased to
TENORMIN 100 mg given as one tablet a day Increasing the dosage beyond 100 mg a day is
unlikely to produce any further benetit
TENORMIN may be used alone or concomitantly with other antihypertensive agents including
thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa
Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe
impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine
clearance falls below 35 ml/min-1 73 m² (normal range is 100-150 ml/min-1 173 m²), therefore, the
following maximum dosages are recommended for patients with renal impairment.

following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml min 1 73 m²)	Elimination Half-life (hrs)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur. HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets. bottles of 100 tablets, and unit-dose packages of 100 tablets and on one side and NDC No 101 embossed on the other side are supplied in bottles and unit-dose packages of 100 tablets and unit-dose packages of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature

References: 1. Data on tile, Stuart Pharmaceuticals 2. Herman RL, Lamdin E, Fischetti JL, Ko HK Postmarketing evaluation of atenolof (Tenormin*) A new cardioselective beta-blocker. Curr Ther Res 1983, 33(1) 165-171. 3. Townley RG. The effect of beta-adrenergic blockade on respiratory function. Primary Cardiol 1980, 6(suppl 1):38-46. 4. Dollery CT. Cardioselective versus noncardioselective beta-adrenergic blocking drugs in therapy of hypertension. Primary Cardiol 1980, 6(suppl 1):64-68. 5. Zacharias FJ. Compansion of the side effects of different beta blockers in the treatment of hypertension. Primary Cardiol 1980, 6 (suppl 1):86-89



MEDICAL SPECIALTIES SPECIALTIES NEWS



The American College of Cardiology

SOME HYPERTROPHIC CARDIOMYOPATHY PATIENT'S INCREASED SUDDEN DEATH RISK IDENTIFIABLE

"It is now possible to identify a subset of patients with hypertrophic cardiomyopathy who have a high rate of laboratory-inducible ventricular fibrillation (VF) and may have an increased risk for sudden death," Dr. Rita M. Watson said.

Dr. Watson, at the National Institutes of Health found that patients with hypertrophic cardiomyopathy who have an abnormal ECG axis and, as one would expect, a history of sudden death "may be at particularly high risk."

Dr. Watson's colleagues included Janine M. Liberati, RN, and Drs. Eben Tucker, Richard O. Cannon, Douglas R. Rosing, Stepehn E. Epstein, and Mark E. Josephson.

"Patients with hypertrophic cardiomyopathy have an increased incidence of sudden death with an annual mortality of 2 to 3%," Dr. Watson, currently Assistant Professor of Medicine, Columbia University College of Physicians and Surgeons, explain. "Furthermore, the documentation of nonsustained ventricular tachycardia on ambulatory monitoring identifies a subset of patients with an even greater risk of 8 to 9% per year."

"I think it is important that the practicing physician known that he can use a 12-lead ECG and possibly a Holter monitor to identify patients with hypertrophic cardiomyopathy whow might die suddenly," Dr. Watson said.

The present trial was designed to identify mechanisms and electrophysiologic predictors of sudden death. Patients "felt" to be at increased risk for sudden death were eligible for the study, Dr. Watson said. These included patients with asymptomatic nonsustained ventricular tachycardia on 24 hours of Holter monitoring, a history of prior sudden death, or a malignant family history of sudden death.

Eighteen patients with a mean age of 36 were selected for enrollment. Fifteen patients had obstructive hyper-

trophic cardiomyopathy; three patients' cardiomyopathy was nonobstructive.

Single, double, and triple extrastimuli and burst pacing were delivered at the right ventricular apex and right ventricular outflow tract at three cycle lengths. Dr. Watson said.

Ventricular fibrillation was induced by programmed ventricular stimulation in 10 of 18 patients, Dr. Watson said. Reproducible VF occured in 8 patients and only in those with nonsustained ventricular tachycardia or a history of sudden death.

Examination of the surface electrocardiogram showed that 5 of the 8 patients with laboratory-inducible VF had a positive R wave (>3mm) in lead a VR in the 12-lead ECG. In addition, half of these 8 patients had abnormalities in the horizontal plane with poor precordial R-wave progression across the precordium. Neither of these findings was seen in any of the patients who had no VF or no reproducible VF.

The investigators also demonstrated inhomogeneous ventricular refractoriness and the appearance of an unusual "double electrogram" with premature stimulation in the patients with VF. Again, this finding was not present in patients who did not have VF or in whom VF was not reproducible.

Dr. Watson found also that the stimulated local ventriculogram in this study population was multiphasic and prolonged, whether or not VF was inducible. That finding, may result, she said, from "the underlying fiber disarray characteristic of hypertrophic cardiomyopathy."

As for treatment, she said, some groups argue that patients should *not* be put on antiarrhythmics that might interfere with conduction, since many of these patients already have conduction system disease, and the efficacy of antiarrhythmics has not been demonstrated. However, a group in England has reported amiodarone is helpful in preventing sudden death. "We can't make any definitive conclusions about antiarrhythmic therapy in these patients," she emphasized, "until these drugs are evaluated in a prospective, controlled study."

48 HOURS OF LOW-DOSE NITROGLYCERIN THERAPY IN MI PATIENTS LIMITS EXPANSION OF INFARCTS

Canadian researchers have found that nitroglycerin therapy for 48 hours during acute myocardial infarction (MI) limits infarct size and decreases the frequency of infarct expansion. Furthermore, the investigators believe that prolonged nitroglycerin therapy might decrease infarct expansion even more.

In a study by Dr. Bodh I. Jugdutt and co-workers at the University of Alberta, Edmonton, infarct exapansion was "strikingly less frequent" in patients receiving lowdose nitroglycerin than in a control group. The drug was particularly useful when started within ten hours after the onset of chest pain.

The findings were described by Dr. Jugdutt, Associate Professor of Medicine at the University of Alberta and

also senior clinical investigator in cardiology and director of the echocardiography research laboratory.

"Infarct expansion, associated with (1) acute left ventricular dilatation and failure, without new ECG or creatine kinase changes, and (2) diastolic stretching, thinning, and shape distortion of the infarcted segment on two-dimensional echocardiography is influenced by infarct size, preload, and afterload," Dr. Jugdutt explained. Since IV nitroglycerin reduces infarct size, preload and afterload, it "might be expected to reduce the incidence of infarct expansion."

In the study, 278 patients admitted to the coronary care unit with suspected acute MI over a recent two-year period were evaluated prospectively.

In order to be eligible for the study, patients had to have cardiac chest pain that began in the previous 12 hours, systolic blood pressure >100mmHg, and heart rate <120 beats per minute. They also had to have evidence of persistent ST segment elevation > 0.2mV in at least two ECG leads, Dr. Jugdutt explained.

One hundred fifty-four patients were assigned at random to nitroglycerin infusion lasting 48 hours in dosages that would reduce mean arterial pressure by 10% but not below 80mmHg. The nitroglycerin dose varied from 4 to 192 mcg per minute. One hundred twenty-four matched controls received a solution of dextrose in water only and no nitroglycerin.

Patients were assigned to therapy that began within ten hours of the onset of pain or ten hours after the onset of pain. Patients were also classified according to infarct location (determined by electrocardiogram).

"Nitroglycerin was most beneficial, regardless of infarct location, in the early subgroup [compared to controls], with greater than 30% improvement in ST segment elevation, left ventricular asynergy, and left ventricular ejection fraction," Dr. Jugdutt noted. "Also, CK infarct size was 34% less in early-than in latenitroglycerin subgroups, and less in those with mean arterial pressure > 80mmHg."

While infarct expansion occurred in 11% of controls, clinical expansion was found in only 2% of nitroglycerin patients.

Among nitroglycerin patients, 12% developed hypotension compared to 27% of controls. Similarly, cardiogenic shock and cardiomegaly were less common in the nitroglycerin patients.

The findings, Dr. Jugdutt, said, clearly indicate that low-dose nitroglycerin therapy can be safely given during acute MI.

Dr. Jugdutt strongly emphasized the importance of careful monitoring during nitroglycerin treatment to avoid hypotension. "While nitroglycerin can reduce arterial pressure by 10% in MI patients," he said, "patients must be continuously monitored and the dose carefully titrated. In this study, blood pressure was monitored by the cuff method and less than 25% of patients required arterial lines or Swan-Ganz catheters."

The Canadian investigator also noted that, while prior studies have reported nitroglycerin to be beneficial only in patients with inferior infarcts, his data, for the first time, demonstrate improvement also in a large group of patients with anterior infarcts.



AMERICAN ACADEMY OF PEDIATRICS

TWO NEW LAB TESTS CAN DETECT MOST COMMON VENEREAL DISEASE

ATLANTA— Two relatively new laboratory tests can detect the most common veneral disease in the U.S.—chlamydia, said an infectious disease expert.

H. Robert Harrison, M.D., Chief of the Clinical Studies Section, Division of Sexually Transmitted Disease, at the Centers for Disease Control, Atlanta, addressed a group at the American Academy of Pediatrics (AAP) Spring Session. He explained that neither test requires growth of the chlamydia organism, as a cell culture test does.

"Lab tests for chlamydia have not been easy to do in the past," Dr. Harrison commented. "Chlamydia takes a long time to grow and it is an expensive test."

Chlamydia, one of the sexually transmitted diseases, is a small bacteria that only grows intracellularly. It can be tramsmitted through the birth canal or through sexual intercourse.

Dr. Harrison said that the two new tests make for an easier and quicker diagnosis, even if the organism is dead.

One test, a flourescent antibody test, involves a cell sample that is stained and examined under a flourescent microscope. The other is an immunological test that uses an enzyme reaction to detect the presence of the chlamydia antigen.

Dr. Harrison said that pediatricians see both ends of the spectrum with chlamydia. A pregnant mother can infect her baby through the birth canal, causing possible conjunctivitis or pneumonia. And, according to the AAP's Committee on Infectious Diseases' Red Book, infecting a baby with chlamydia also can cause blindness.

In addition, pediatricians need to be aware of chlamydia in teenagers, as more pediatricians are becoming adolescent gynecologist today, Dr. Harrison said.

Dr. Harrison, also a clinical associate professor of pediatric at Emory University School of Medicine, Atlanta, said that neither test is a specific culture diagnosis, and therefore, it is possible to have a false-positive test result.

"These tests have advantages over the cell culture test but they also have limitations," he said. With the flourescent test, very careful preparation of slide and an expert reading is essential, Dr. Harrison explained. The enzyme reaction test is less proven as an effective screening technique and hasn't been evaluated as much as the other test. Medical Specialties News Vol. 77 Núm. 8

PREVENTING TEEN PREGNANCY: CHANGE MALE ATTITUDES

A procedure as simple as the dispensing of condoms by physicians and more attention to the male's attitude toward birth control may successfully motivate contraceptive use by male teens and help lower the number of teen pregnancies in the U.S.

A study has found, however, that teen fathers think contraception is ineffective and don't believe in it.

"The barriers to the use of birth control appear to be mostly attitudinal, rather than financial or due to a lack of availability," reported researchers at the University of Tennessee, Memphis, in the April issue of *Pediatrics*, the journal of the American Academy of Pediatrics (AAP).

The mean age of first sexual intercourse (12.5 years) in this report was the same for the two groups studied—teen fathers, and teens of the same age who weren't fathers. The researchers found that knowledge about sex, pregnancy and contraceptive use was equal in both groups as well. "Nearly half (of both groups) felt that birht control was ineffective and that the girl/woman would get pregnant anyway," they said.

The researchers, Frederick Rivera, M.D. and Patrick Sweeney, M.D., studied two hundred boys between the ages of 14 and 19 at the University's Prenatal Clinic. Both groups consisted primarily of urban black teens from a low socieconomic group.

Most of the males reported feeling embarrassed to ask for contraceptives at a family planning clinic because: most of the professionals there were women, lack of privacy, and that the other clinic users were mostly female.

The researchers found differences, however, in the two groups' attitudes towards the outcome of teen pregnancy. For the teen fathers, having a baby as a teenager was accepted as a normative, cultural experience.

The doctors found teen fathers seemed to come from an environment where teen pregnancy was common—many of their mothers, brothers and sisters had been or were teenage parents. These boys came from large, primarily female-headed families where the role model undoubtedly contributed to (their) perception that teenage pregnancy was not necessarily undesirable or disruptive of their lives now or in the future.

Many of the teens who were not fathers thought that pregnancy would disrupt their plans for school, a job and marriage. In addition, they thought their families' and friends' reactions would be negative. The teen fathers' views were the opposite in both cases.

This study is one of the few that focused on the teenage father. The researchers concluded that successful contraceptive use depends on changing the teen's beliefs and perceptions, as well as parents' and peers'.

RECOMMENDATIONS MADE FOR NEW H. FLU VACCINE

The American Academy of Pediatrics (AAP) has issued recommendations for using a new vaccine which

protects against Hemophilus influenzae type B (Hib).

A major cause of serious, invasive infections in infants and children (including meningitis), Hib infection incidence is highest in infancy. The exception is epiglottitis, when the mean age is 44 months.

Called b-Capsa I, the vaccine has been recommended for all children 24 months old. It may also be given to the sixth birthday, and for those as young as 18 months in high risk groups, such as those in day care centers, says the AAP and the Centers for Disease Control's Advisory Committee on Immunization Practices.

"The number of serious infections caused by Hemophilus at this time in the United States is about the same number of serious illnesses that the polio virus caused before the advent of polio vaccine," says Philip Brunell, M.D., chairman of the AAP's Committee on Infectious Disease. "The new vaccine is a major breakthrough."

However, this vaccine is not the final Hib antigen. Other vaccines which could given protection to children younger than 18 months are being developed and evaluated, according to the CDC.

"Hib occurs most frequently in children between six and twelve months of age," says Dr. Brunell. "Ideally, this vaccine could be given to younger infants."

He adds that if the new vaccine is given to all children in the U.S. now, it will eliminate about 25 percent of the disease caused by the organism. In addition, future vaccines now being tested could eliminate 90 percent of the disease caused by hemophilus. The Academy recommends:

- * Immunization with Hib vaccine for all children at 24 months. For those who don't get the vaccine at this time, immunization through the 6th birthday will prevent cases of the disease. The need for additional doses has not been established.
- *For children 18-23 months old, there are insufficient data upon which to base a recommendation regarding vaccine administration. If vaccine is given at this time, it should be recognized that the likelihood of protection is uncertain. Parents should be aware of this, because additional immunization may be required at 24 months or later.
- * Vaccine is not recommended for children less than 18 months of age.
- * Children, even those other than 5 years of age, who have chronic illnesses with increased risk for Hib disease should be given a single vaccine dose. These illnesses include anatomic or functional asplenia, including sickle cell disease or children who have undergone splenectomy.
- * Children with immunoglobulin synthesis deficiencies probably will not benefit from the vaccine. As in the past, they should receive periodic doses of immuneglobulin.

PROLONGED INFANT APNEA: AAP GUIDELINES SET

Prolonged infantile apnea, often defined as the cessation of breathing for at least 20 seconds, is a condition

that some say might be linked to sudden infant death syndrome (SIDS).

However, since no causal relationship has yet been established and the etiology and optimal management of prolonged apnea are not clear, the American Academy of Pediatrics (AAP) Task Force on Prolonged Infant Apnea has issued guidelines to clarify which treatments can be implemented (e.g., monitoring technology) with available medical knowledge.

Writing in the July issue of *Pediatrics*, the journal of the American Academy of Pediatrics, the task force said infants who have had an episode of prolonged apnea are perceived by parents and physicians as "having experienced a life-threatening event and being at risk for another."

Prolonged apnea, they continued, can be a symptom of many disorders, including infection, seizure, airway abnormalities, hypoglycemia or other metabolic problems, anemia (in preterm infants), gastroesophageal reflux, impaired regulation of breathing during sleeping and feeding, and abuse.

The task force mentioned that prolonged apnea can also include a briefer episode of apnea associated with bradycardia, or pallor. Brief episodes of apnea are a normal occurrence in infants, but prolonged apneic episodes may lead to morbidity— though rerely mortality.

To correct the emotional and sometimes erroneous information about apnea and SIDS, the task force voice concern "that the vast majority of infants with prolonged apnea are not victims of SIDS; most SIDS victims were never observed to have had prolonged apnea prior to the terminal event."

They did say, however, that there is an indication that preterm infants as a group and perhaps siblings of infants who were victims of SIDS are at somewhat increased risk.

To update 1978 recommendations from a similar AAP task force, the present group emphasized the following major points regarding prolonged apnea:

- 1) Physicians must be responsible for all evaluations and management of infants with prolonged apnea.
- 2) A thorough initial evaluation to determine possible treatable causes of apnea is mandatory.
- 3) Asymptomatic infants, including those with previous apnea or those with statistically increased risk of SIDS, may be candidates for home monitoring, but there are no tests that will reliably determine risk status. Physicians should prescribe monitoring if they feel that method of management is in the best interest of their patient.
- 4) Monitoring technology is still being developed and refined. Most authorities feel that both cardiac and respiratory functions should be monitored electronically. Some feel monitoring cardiac function alone is equally effective. Ability to produce a permanent record, when needed, is desirable.
- 5) When home monitoring is elected, parents should be advised that monitors cannot guarantee against SIDS. Monitor advertisements that assure absolute protection should be condemned for unscrupulous attempts to profit from the situation. A plan for

- periodic re-evaluations and termination of monitoring should be developed and explained to the parents.
- 6) Because the etiology and optimal management of prolonged apnea are not clear and because a causal relationship between prolonged apnea and SIDS has not been established, continued research is essential.

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SOCIOS NUEVOS



ACTIVOS

Carrero Nieves, Evelyn, MD - Universidad de Puerto Rico, 1982, Anestesiología. Ejerce en Hato Rey.

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Falcón Matos, Carlos A., MD - Universidad Central del Caribe, Cayey, 1981, Fisiatría. Ejerce en Guaynabo.

Figueroa Sepúlveda, René, MD - Universidad de Sevilla, Facultad de Medicina, España, Pediatría. Ejerce en Juana Díaz.

González Morales, Orlando, MD - Universidad Central del Este, República Dominicana, 1977, Cirugía General. Ejerce en Río Piedras.

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Velilla Iglesias, Manuel, MD - Universidad Autónoma de Guadalajara, México, 1977, Obstetricia y Ginecología. Ejerce en Puerto Nuevo.

INTERNOS-RESIDENTES

Guzmán Alvarez, Hiram, MD - Escuela de Medicina, Universidad Central del Caribe, Cayey, 1981, Medicina Interna.

Montalván Ruiz, Avelino, MD - Facultad de Medicina de Cadiz, España, 1979, Psiquiatría.

REINGRESOS

Labat, Ricardo Alberto, MD - Universidad de Cuyo, Argentina, 1964, Cirugía. Ejerce en Caparra Heights.

Ocasio Rodríguez, Arnaldo, MD - Universidad de Salamanca, España, 1966, Medicina General. Ejerce en Barceloneta.



ROUTINE PREOPERATIVE TESTS MAY NOT BE NEEDED

Most routine laboratory tests ordered prior to surgery may not be needed, according to a study published in the *Journal of the American Medical Association*. Researchers from the University of California, San Francisco, say 60 percent of the tests in their study of 2,000 patients "would not have been performed if testing had only been done for recognizable indications."

Furthermore, only 0.22 percent of those tests revealed abnormalities that might influence perioperative management. "Chart review indicated that these few abnormalities were not acted on nor did they have adverse surgical or anesthetic consequences," say Eric B. Kaplan, MD, and colleagues. They conclude: "In the absence of specific indications, routine preoperative laboratory tests contribute little to patient care and could be elimiated."

Acted upon, their conclusion could exert a major influence on the costs of medical services. The researchers estimate that patient charges would decrease \$147,000 per year at their institution alone.

Comments JAMA George D. Lundberg, MD, "No one quibbles about doing appropriate laboratory testing in the presence of a clinical indication. But in these days of increasing efforts at controlling costs and insisting on appropriate use of resources, the unindicated, routine preoperative laboratory test may well be something that we can do without."

Lundberg points out there are many reasons why physicians order laboratory tests. Among them: screening, peer pressure, personal reassurance, ease of performance with ready availability, hospital policy, medical-legal need, documentation, hospital profit, curiosity, insecurity, habit and establishment of a baseline.

The study by Kaplan and colleagues was a retroactive evaluation of tests performed on patients admitted to their teaching hospital for elective surgery, and therefore was limited to the information that was available in hospital charts. "Such information is not always complete," lundberg says.

"We would like to see this retrospective study followed by appropriately designed prospective studies that could define proper practice," he adds. "Meanwhile, the apparent cost/risk/benefit elements that are reported herein should ease the minds of those physicians who may wish to do prospective studies and should militate against a significant professional liability risk for such studies."

JAMA June 28, 1985

NEW SURGICAL STRATEGIES PROPOSED FOR BREAST CANCER TREATMENT

Successful treatment of breast cancer through lumpectomy instead of mastectomy calls for new surgical strategies, including reappraisal of breast biopsy, asserts Bernard Fisher, MD, of the University of Pittsburgh. Fisher's observations appear in JAMA, with two other articles that discuss the attendant risks and benefits of mastectomy, lumpectomy and radiation therapy.

Fisher's recommendations are prompted by results of a recent study documenting similar five-year survival rates among women who had mastectomies and those who had lumpectomies followed by radiation therapy. "Those observations, should they continue as described, indicate that lumpectomy plus radiation can be justifiably employed instead of total mastectomy for the treatment of a large proportion of women with primary breast cancer," he says. "Experience acquired with lumpectomy has altered not only my views and policies relative to breast biopsy but also my entire approach to breast cancer surgery."

Fisher says that a one-stage procedure was standard for diagnosing and treating breast cancer until recently. With the patient under general anesthesia, a biopsy was done and if the tissue was malignant a mastectomy was performed. With increasing awareness of less radical surgery, more patients began having biopsies done on an outpatient basis, and seeking second opinions before undergoing surgery. Fisher points out that in both cases, little consideration was given to proper placement of incisions for biopsies or for ensuring that biopsy specimen margins were tumor-free, mastectomies were usually performed when the lesion was malignant.

Fisher says that ideally, if the lesion is palpable and a cytologist is available, a fine-needle aspiration or coreneedle biopsy should first be performed to examine the cells. If this examination is inconclusive or cannot be done, then an open biopsy should be performed as if it were a lumpectomy (making sure the specimen margins are grossly free of tumor), and if the tissue is malignant, the axillary nodes should then be removed. "Prior to such an intervention, however, it should be decided... whether the patient can be treated by a breast conserving operation or whether she will require a mastectomy if the lesin in question is found to be malignant."

By discussing the alternatives and/or obtaining a second opinion before intervention, then by treating biopsy as a lumpectomy, Fisher says women will probably require only one surgical procedure. He concludes, "In any circumstance where breast conservation is feasible, the operation carried out to establish the definitive *diagnosis* of a breast lesion becomes the definitive *treatment* along with axillary dissection."

In a related article, Roberto Lipsztein, MD, and colleagues of Mount Sinai Medical Center, New York, say that since lumpectomy followed by radiation therapy is becoming an increasingly accepted treatment for breast cancer, the risks of radiation need to be reevaluated. They note that long-term exposure to radiation can prevent, but also can cause cancer. "An increase in breast cancer attributable to radiation exposure is generally not observed until ten years after exposure," they say, noting that the incidence of recurrence of tumors in women should be followed carefully after lumpectomy. The researchers say that most other harmful effects of radiation are transient and not severe.

Commenting editorially, Jerome A. Urban, MD, of New York, notes, "Patients must be informed of the relative advantages and disadvantages of various therapeutic options available... Mastectomy, obviously, results in the loss of the breast, but this can be balanced by the fewer physical complaints (pain or stiffness from radiation), lack of long-term complications, improved local control, and, most likely, improved long-term survival... Patients' priorities vary, and they must be given an opportunity to select the treatment that is most attractive to them."

JAMA June 28, 1985

SPOUSE IMMUNITY TO SPERM MAY CAUSE INFERTILITY

Infertility in some women may be caused by an immune reaction to sperm cells of their husbands, according to a report in the *Journal of the American Medical Association*.

Patricia M. McShane, MD, and colleagues of Harvard Medical School studied serum samples from 14 infertile women and nine fertile women to observe how certain blood cells (leukocytes) would react to sperm. None of the infertile women nor their husbands showed by obvious medical cause for infertility. "Five (36 percent) of 14 infertile patients but none of nine fertile volunteers responded significantly to sperm in this assay," the researchers say. "These data provide additional evidence consistent with the possibility that cellular immunity to sperm-specific antigen(s) functions in the primary pathogenesis of infertility in some women."

The researchers say that the cells from the 14 infertile women generated significantly greater inhibitory action to sperm than did cells from the nine fertile women. The study also showed that the five infertile women with significant immune responses were from the group of 11 who had shown positive results on previous indirect tests for antibody to sperm. In this study, however, neither IgG nor IgM were detected in any of the subjects.

The researchers remain cautious in interpreting their findings: "The demonstration of cellular responsiveness

to sperm does not necessarily implicate this reaction in the primary pathogenesis of infertility. It is possible that this finding represents a secondary phenomenon, which is a result rather than a cause of infertility."

Approximately 15 percent of couples have involuntary infertility, the report notes, and some of these cases remain unexplained. The researchers say their data suggest there is an association between an abnormal immune response to sperm and infertility, and that attempts to influence fertility by altering the immune system merit further investigation.

JAMA June 28, 1985

IMPROVED RESULTS REPORTED IN ADULT LEUKEMIA

Encouraging and significant improvement in longterm survival among adult patients with acute leukemia are reported from the Southwest Oncology Group based in San Antonio, Texas. The group has been studying chemotherapy for leukemia patients since the 1970s, and says its most recent study, involving 216 patients, achieved the highest overall survival time thus far. Fiveyear survival for all patients increased from 4 percent to 14.3 percent. Percentage of patients achieving five year survival and complete remission increased from 15 percent to 26 percent. "Data such as these suggest that some adults with acute leukemia are being cured," write James S. Hewlett, MD, of the Cleveland Clinic Foundation, and study colleagues in the June Archives of Internal Medicine. Drugs used in a study were vincristine sulfate, cytarabine, and prednisone.

BIRTH DEFECTS ASSOCIATED WITH EXPOSURE TO ANTICONVULSANTS

Anticonvulsant therapy may cause major abnormalities of the central nervous system, according to a study in the Archives of Pathology and Laboratory Medicine. Jill E. Trice, MD, of the University of California-San Diego, and Mary Ambler, MD, of Brown University in Providence, R.I., report autopsy findings of a three-month-old infant exposed in utero to anticonvulsants. Abnormalities include bilateral encephaloceles, ventricular abnormalities, and defective neuronal migration—all severe brain defects. The infant's 19-year-old mother had been treated with phenytoin during the first two trimesters of pregnancy to control episodes of hyperventrilation.

NEW PHOTODYNAMIC THERAPY FOR HEAD AND NECK CANCER

A study from Ohio State University in Columbus demonstrates the safety of a new, photodynamic therapy for cancers of the head and neck. Reporting in the June

Archives of Otolaryngology, David E. Schuller, MD, and colleagues say they studied the technique with a group of 24 patients with recurrent and/or metastic cancers, using hematoporphyrin and argon beam laser. "The conclusion of this experience is that photodynamic therapy is an attractive new modality because of its specificity for treating only tumor tissue," they say. "The methodology is indeed feasible for head and neck cancers and it seems to be well tolerated, with a low toxicity."

GENES INFLUENCE HEART RESPONSE TO EXERCISE

Changes in cardiac dimensions associated with endurance training are shaped in part by one's genetic make-up, according to a study reported in JAMA.

Researchers Fernand Landry, PhD, of Laval University, Quebec, and colleagues measured aerobic capacity and heart dimensions in 20 sedentary persons and ten pairs of identical twins (same genotype) before and after a 20-week endurance training program. Maximal oxygen uptake (aerobic capacity) increased significantly in both groups: by 30 percent in the sedentary group and by 13 percent among the twins, the researchers say. But statistically significant changes in the heart itself, such as increases in left ventricular diameter, posterior wall and septal thicknesses, left ventricular end-diastolic volume and left ventricular mass occurred only in the sedentary group.

The study provides new evidence that regular exercise can result in increased size and strength of the heart. "Results... confirm the hypothesis that moderate yet statistically significant degress of hypertrophy of the left ventricle are likely to occur with intensive exercise training," the researchers say.

The most striking finding was that after training, the cardiac characteristics within each pair of twins were more alike than before training. However, twin pairs showed marked differences from other, unrelated twins. "Clearly, there seems to be a genotype-dependent adaptive mechanism at work," the researchers say.

"Even though no mean changes were found in heart dimensions, it was observed that posttraining intrapair resemblance had become markedly higher than pretraining resemblance."

The researchers say their study is unique because it measured aerobic and cardiac changes in previously sedentary persons and because it evaluated genetic predisposition to heart enlargement. They conclude, "The present study shows that cardiac dimensions... are amenable to significant modifications with intensive exercise training in previously inactive subjects under conditions causing a major increase in maximal aerobic power. In addition, data from monozygotic (identical) twins suggest that the response of cadiac structures to training is perhaps determined by the genotype."

JAMA July 5, 1985

TIMOLOL PREVENTS EYE PRESSURE ELEVATION AFTER SURGERY

Treatment with 0.5 percent timolol following cataract surgery frequently prevents intraocular pressure elevation, according to a controlled study from Harvard Medical School that appears in the July Archives of Ophthalmology. Claudia U. Richter, MD, and colleagues point out that IOP elevation is a frequent and potentially catastrophic complication of neodymium-YAG laser cataract surgery, and say they studied the eyes of 32 patients treated with timolol, 2 percent pilocarpine, or normal saline five and 30 minutes after surgery to compare effectiveness of prevention. Pressure elevation was only 1 +or-2 mm Hg with timolol, while other readings were 5 +or-3 and 8 +or-2 respectively. "This prophylactic therapy does not provide complete protection," the researchers caution, but it does clearly minimize intraocular pressure elevations.

PERTUSSIS A MISSED DIAGNOSIS: STUDY

An eight-year-review of patients seen at the Upstate Medical Center in Syracuse, N.Y., for treatment of whooping cough showed that 55 percent were misdiagnosed at admission, according to a report in the July American Journal of Diseases of Children. Bronchiolitis and/or pneumonia were frequently listed as diagnoses, report Juan Sotomayor, MD, and colleagues from the State University of New York, Syracuse. Accurate diagnosis of pertussis, or whooping cough, is needed not only to allow specific treatment, but also to prevent transmission to other infants, the researchers say. Commenting editorially, Vincent A. Fulginiti, MD, and C. George Ray, MD, Tucson, observe, "We should never allow ourselves to become complacent about problems that are solvable, if only we remember their nature and use the tools available to us to establish the correct diagnosis."

MULTIPLE EXAMINERS BETTER IN SPORTS MEDICINE

The preparticipation athletic examination might best be performed by a team of physicians at multiple stations, according to a study from the Medical College of Georgia in Augusta. Robert H. DuRant, MA, and colleagues compared that method with examinations by personal physicians in a study involving 922 student athletes. "Multiple-examiner station examinations disclosed significantly more abnormal findings in the spine, hips, thighs, kness and ankles than the single-physician examinations did," they say in the July American Journal of Disease of Children. Responsibility for one single component in the physical exam probably accounts for the difference, they say.

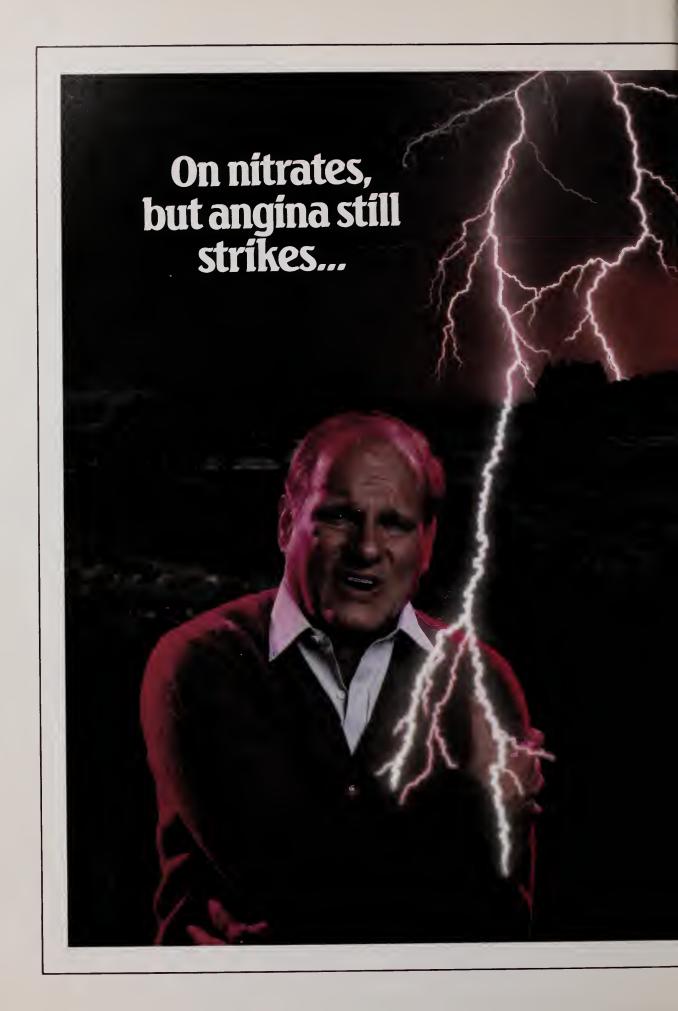
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Contraindications: Severe left ventricular dysfunction (see Warnings), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction < 30% or moderate to severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. (See Precautions.) Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before ISOPTIN is used. (Note interactions with digoxin under Precautions.) ISOPTIN may occarrically produce beta residue to the second controlled with optimum doses. sionally produce hypotension (usually asymptomatic, orthostatic, mild and controlled by decrease in ISOPTIN dose). Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations may disappear even with continued treatment; how-ever, four cases of hepatocellular injury by verapamil have been proven by re-challenge. Periodic monitoring of liver function is prudent during verapamil therapy. Patients with atrial flutter or fibrillation and an accessory AV pathway (e.g. W-P-W or L-G-L syndromes) may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion, which has been used safely and effectively after ISOPTIN Because of verapamil's effect on AV conduction and the SA node, 1° AV block and transient bradycardia may occur. High grade block, however, has been infrequently observed. Marked 1° or progressive 2° or 3° AV block requires a dosage reduction or, rarely, discontinuation and institution of appropriate therapy depending upon the clinical situation. Patients with hypertrophic cardiomyopathy (IHSS) received verapamil in doses up to 720 mg/day. It must be appreciated that this group of patients had a serious disease with a high mortality rate and that most were refractory or intolerant to propranolol. A variety of serious adverse effects were seen in this group of patients including sinus bradycardia, 2° AV block, sinus arrest, pulmonary edema and/or severe hypotension. Most adverse effects responded well to dose reduction and only rarely was verapamil discontinued. Precautions: ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patients should be carefully monitored to avoid over- or under-digitalization. ISOPTIN may have an additive effect on lowering blood pressure in patients receiving oral antihypertensive agents. lowering blood pressure in patients receiving oral antihypertensive agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should prob-ably be avoided, since significant hypotension may result. Clinical experience with the concomitant use of ISOPTIN and short- and long-acting nitrates suggest beneficial interaction without undesirable drug interactions. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigénic potential, and verapamil was not mutagenic in the Ames suggest a tumorigenic potential, and verapamii was not mutagenic in the Arries test. *Pregnancy Category C*: There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR < 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nature (1.6%), elevations of liver enzymes have been reprotedtion (6.3%), nausea (1.6%), elevations of liver enzymes have been reported. (See *Warnings*.) The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: ecchymosis, bruising, gynecomastia, psychotic symptoms, confusion, paresthesia, insomnia, somnolence, equilibrium disorder, blurred vision, syncope, muscle cramp, shaking ness, claudication, hair loss, macules, spotty menstruation. How Supplied: ISOPTIN (verapamil HCI) is supplied in round, scored, film-coated tablets containing either 80 mg or 120 mg of verapamil hydrochloride and embossed with "ISOPTIN 80" or "ISOPTIN 120" on one side and with "KNOLL" on the reverse side. Revised August, 1984.



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Indications: Effective in all types of insamnia characterized by difficulty in falling asleep, frequent nacturnal awakenings and/ar early marning awakening; in patients with recurring insamnia ar paar sleeping habits; in acute ar chranic medical situations requiring restful sleep. Objective sleep laboratory data have shawn effectiveness for at least 28 cansecutive nights of administration. Since insamnia is aften transient and intermittent, pralanged administration is generally nat necessary ar recammended. Repeated therapy shauld anly be undertaken with appropriate patient evaluation.

Contraindications: Known hypersensitivity ta flurazepam HCl, pregnancy Benzadiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of cangenital malfarmations associated with benzadiazepine use during the first trimester. Warn patients of the patential risks to the fetus should the passibility of becaming pregnant exist while receiving flurazepam. Instruct patient a discantinue drug prior to becaming pregnant. Cansider the passibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about passible cambined effects with alcahal and other CNS depressants. An additive effect may accur if alcahal is cansumed the day fallowing use far mightlime sedation. This patential may exist far several days fallowing discantinuation. Cautian against hazardaus accupations requiring camplete mental alertness (e.g., aperating machinery, driving). Patential impairment of performance at such activities may accur the day tallowing ingestion. Nat recammended far use in persans under 15 years of age. Though physical and psychological dependence have not been reparted an recammended dases, abrupt discantinuation should be ovaided with gradual tapering of dasage for thase patients an medication far a pralanged periad of time. Use cautian in administering to addiction-prane individuals ar those wha might increase dasage.

Precautions: In elderly and debilitated patients, it is recammended that the dasage be limited to 15 mg to reduce risk of aversedation, dizziness, confusion and/or ataxio. Consider patential additive effects with other hypnatics ar CNS depressants. Emplay usual precautions in severely depressed patients, or in those with latent depression ar suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drawsiness, lightheadedness, staggering, ataxia and falling have accurred, parlicularly in elderly ar debilitated patients. Severe sedatian, lethargy, disarientation and cama, probably indicative af drug intalerance ar averdasage, have been reparted. Alsa reparted. headache, heartburn, upset stamach, nausea, vamiting, diarrhea, canstipation, Gl poin, nervousness, talkativeness, apprehensian, irridability, weakness, palpitations, chest pains, bady and joint pains and GU camplaints. There have alsa been rare accurrences af leukapenia, granulacytapenia, sweating, flushes, difficulty in facusing, blurred visian, burning eyes, faintness, hypotensian, shortness of breath, pruritus, skin rash, dry mauth, bitter taste, excessive salivation, anarexia, eupharia, depressian, slurred speech, canfusian, anatexia, eupharia, and alkaline phasphatase, and paradaxical reactions, e.g., excitement, stimulatian and hyperactivity.

Dosage: Individualize far maximum beneficial effect. *Adults*: 30 mg usual dasage, 15 mg may suffice in same patients. *Elderly ar debilitaled palients*: 15 mg recammended initially until response is determined.

Supplied: Capsules cantaining 15 mg ar 30 mg flurazepam HCl.



#1 FOR SLEEP

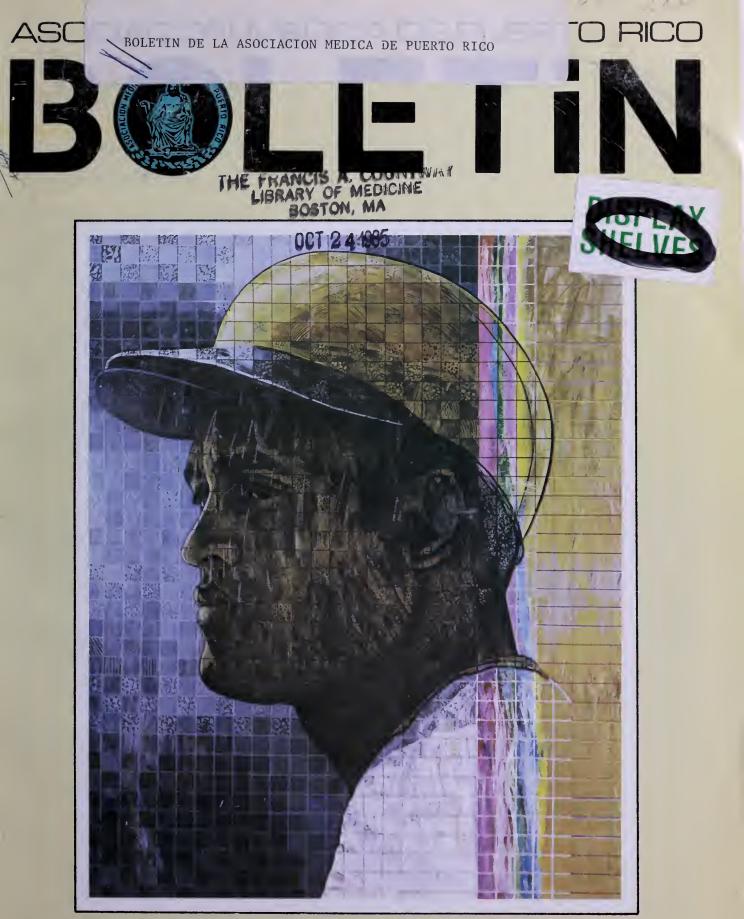
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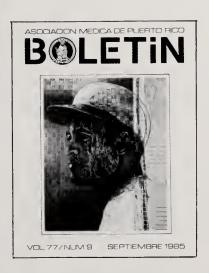


os artículos que aparecen publicados en este número, en su mayoría trabajos originales por investigadores locales cubren temas de trascendencia clínica. El artículo del Dr. Manuel Miranda, Director del Departamento de Oftalmología de la Escuela de Medicina de la Universidad de Puerto Rico, presenta los factores más importantes que se han publicado sobre los estímulos retinales en la acomodación así como la importancia del contraste y la iluminación. El artículo sobre la utilidad de la proteína C-reactiva en la diferenciación de la meningitis bacteriana y viral refleja la experiencia local en ese sentido. Es un trabajo sencillo, factible en un ambiente de recursos limitados y que provee información de trascendencia clínica significativa. Nos consta que estudios de este tipo se están llevando a cabo constantemente en los centros principales de enseñanza médica en nuestro país. Esperamos que la publicación del trabajo de los Dres. Betancourt y Montes sirva de estímulo a otros investigadores jóvenes a preparar sus trabajos con el fin de divulgar sus resultados y comentarios a nuestros lectores.

El artículo del Dr. Rigau-Pérez sobre el Control de la Hipertensión en Puerto Rico comenta las metas alcanzadas en ese sentido y las estrategias para lograr aquellas aún en vías de alcanzar. Relacionado con otro factor de riesgo de enfermedades coronaria, el Boletín reproduce un artículo de "Heart Beat", el órgano oficial de la Sociedad Internacional y Federación de Cardiología, sobre la ateroesclerosis en niños y adolescentes. Se hacen recomendaciones prácticas sobre el control y la prevención de este factor de riesgo tan importante. Es sabido que el proceso aterosclerótico tiene sus comienzos en la niñez por lo cual todos los esfuerzos de prevención primaria para su inhibición deben iniciarse en la edad pediátrica.

Milavieni Ino

Rafael Villavicencio, MD, FACC Presidente Junta Directora Boletín Asociación Médica de Puerto Rico



NUESTRA PORTADA

"Roberto" óleo en lienzo de 6 pies por 4 pies es un homenaje de nuestro pintor Carlos Irizarry a un puertorriqueño que fue tan buen patriota como deportista; Roberto Clemente. La obra marca una pausa agradable en los temas frecuentemente explosivos del artista. Carlos Irizarry, "el Pintor de la Puertorriqueñidad", nació hace 46 años en Santa Isabel y ha logrado llevar al lienzo, con gran éxito artístico, grandes realidades de Puerto Rico como en la obra "La Transculturación del Puertorriqueño".

La solución a todos los grandes problemas que avasallan nuestro pueblo no es posible si cada puertorriqueño no hace lo que le toca hacer dando su mayor esfuerzo. No debemos jamás olvidar el "Legado de Roberto" que encierra la siguiente cita de su discurso en un banquete de premiación deportiva en la ciudad de Nueva York, actividad en la cual se le reconoció como el mejor orador de la noche:

"A veces yo me pregunto de donde saco energías para dar el máximo de mi esfuerzo en cada jugada de cada juego en que participo. Y es que yo estoy convencido que todo lo que hago bien ayuda a mis compatriotas puertorriqueños y todo lo que hiciera mal los atrasaría en realizar sus grandes y legítimas aspiraciones."

La mirada lejana y triste de Roberto es otra joya más para el tesoro de la plástica puertorriqueña.

La reproducción de esta obra de arte en nuestra portada ha sido posible gracias a la gentileza del Dr. Angel L. Rodríguez-Rosado y del autor.



83ra. CONVENCION ANUAL

Centro de Convenciones del Condado Noviembre 6 a 11

Programa de Educación Médica Contínua Tentativo

MIERCOLES, 6 DE NOVIEMBRE

(Todo el día: Registro)

2:00 P.M. - Torneo de Golf - Dr. Ricardo Méndez Bryan

7:00 P.M. - Sesión Inaugural

JUEVES, 7 DE NOVIEMBRE

(Continúa el Registro de Participantes)

A.M.

J-2 — Medicina Industrial - Dr. C. Villafaña

J-2 — Sexualidad - Dr. A. López-Deynes

J-3 — Resuscitación Cardiopulmonar

J-4 — Hematología - Dr. Salomón Asmar

J-5 — Medicina Nuclear - Dr. Roberto Bordewick

P.M.

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J-7 — Medicina Física y Rehabilitación - Dr. Rafael Sein

J-8 — Urología - Dr. Antonio Puras

J-9 — Reumatología - Dr. Edwin Mejías, Dr. Salvador Vilá

J-10 — Computadoras - Sr. Jorge Calaf

VIERNES, 8 DE NOVIEMBRE A.M.

V-1 — Organización y Administración de la Oficina Médica
 Dr. Juan R. Colón Pagán

V-2 — Resuscitación Cardiopulmonar

V-3 — Medical Evaluation for Disability Claims Dr. T.G. Heibert

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V-5 — Oncología - Dr. Luis Báez-Díaz

P.M.

V-6 — Medical Evaluation for Disability Claims Dr. T.G. Heibert

V-7 — AIDS - Dra. María Santaella

V-8 — Resuscitación Cardiopulmonar

V-9 — Análisis Transaccional

Dr. Héctor Feliciano y Sra. Nereida Feliciano

V-10 - Cardiología - Dr. Félix Cortés

Viernes 12 M.

Conferencia Magistral Dr. Isaac González Martínez Dr. Franco Muggia - Profesor de Medicina y Director de Hematología/Oncología, New York University

SABADO, 9 DE NOVIEMBRE A.M.

S-1 — Temas Libres - Dr. Carlos Ramírez Ronda, Dr. Edgardo Hernández

S-2 — Resuscitación Cardiopulmonar

S-3 - Hipertensión - Dr. Rafael Ramírez-González

S-4 — Ginecología - Dr. Jose A. Roure/ Dr. Arsenio Comas

S-5 - Medicina de Adolescente - Dr. F. Ramos-Isern

P.M.

S-6 — Medicina Industrial - Dr. Carlos Villafaña

S-7 — Psiquiatría - Dr. William Galindez

S-8 — Temas Libres - Dr. Rafael Cox, Dr. Rafael Rodríguez-Servera

S-9 — Resuscitación Cardiopulmonar

S-10 — Sexualidad - Dr. Alejandro López Deynes

CAMARA DE DELEGADOS TODO EL DIA Actividad Social: Fiesta Tropical 7:30 P.M.

DOMINGO, 10 DE NOVIEMBRE A M.

D-I — Relaciones Públicas - Sra. Moraza, A.P.R.

D-2 — Resuscitación Cardiopulmonar

D-3 — Medical Evaluation Disability Claims Dr. T.G. Heibert

D-4 — Enfermedades Infecciosas - Dra. Julie Rodríguez

D-5 — Pediatría - Dr. Rafael Villavicencio

D-6 - Psiquiatría - Dr. Robert Stolberg

P.M.

D-7 — Planificación Familiar y Fecundidad en Puerto Rico
 Dra. Rafaela Robles

D-8 — Medical Evaluation Disability Claims Dr. T.G. Heibert

D-9 — Dermatología - Dr. Jorge Sánchez

D-10 — Reembolso Medicare S.S.S. - Lic. Frank Fournier

D-11 — Resuscitación Cardiopulmonar

D-12 — Neumología - Dr. Ramón Figueroa Lebrón

DOMINGO 12:00 M.

Conferencia Magistral Dr. E. Fernández García

Dr. Sol Katz - Director Neumología, Universidad de Georgetown

LUNES, 11 DE NOVIEMBRE

9:00 - 11:30 A.M. — 2 sesiones de C.P.C.

Dr. Gustavo Ramírez de Arellano

Dr. Eliud López

11:30 A.M. hasta 1:00 P.M. -

Conferencia Magistral Dr. Ramón M. Suárez,

Dr. Elliot Rappaport

1:00 P.M. — TOMA DE POSESION



LOS OBJETIVOS DE SALUD PARA ESTADOS UNIDOS EN 1990 Y SU APLICACION A PUERTO RICO.

El Control de la Hipertensión en Puerto Rico: Progreso hacia los Objetivos Nacionales de Salud para 1990 (IV).

José G. Rigau-Pérez, M.D., F.A.A.P.* Ivonne M. Rodríguez-Conesa, B.S.** Juan J. Vázquez-Bauzá, B.S.**

Resumen: De las nueve metas nacionales de salud para 1990 referentes al control de la alta presión arterial, sólo una está siendo perseguida en Puerto Rico, la que pide que se indique el contenido de sodio y calorías en la rotulación de los alimentos. Las otras metas necesitan trabajarse desde el plano más básico. La obtención de estos objetivos en Puerto Rico, al igual que en otros estados, exige la cooperación de diversas instituciones gubernamentales, académicas y cívicas.

n 1980 el Servicio de Salud Pública de los Estados Unidos ("U.S. Public Health Service") publicó unas metas para el mejoramiento de la salud de los habitantes del país en los próximos diez años.1 Quince asuntos prioritarios fueron identificados: control de la hipertensión, planificación familiar, embarazos y salud infantil, inmunizaciones, enfermedades de trasmisión sexual, control de agentes tóxicos, seguridad y salud ocupacional, prevención de accidentes y control de traumatismos, fluorización y salud dental, vigilancia y control de enfermedades infecciosas, fumar y el deterioro en la salud, abuso de alcohol y drogas, nutrición, acondicionamiento físico y ejercicio, control del estrés y el comportamiento violento. Dentro de cada área se especificaron los objetivos a alcanzar para 1990. Estos objetivos (226 en total), planteados de manera mesurable, se desarrollaron en consulta con más de quinientos expertos de los sectores público y privado, que representaban agencias de salud federales, estatales y locales, grupos de consumidores, organizaciones de voluntarios y profesionales de salud. Las metas se establecieron tomando en cuenta las

tendencias actuales de factores pertinentes, tales como cambios demográficos, estilos de vida y la disponibilidad de fondos, y detallando lo que se asumió ocurriría con estos factores en la década de 1980 a 1990. Las metas han de alcanzarse por los esfuerzos de toda la gama de agencias e instituciones públicas y privadas, de personas y comunidades, y no se han establecido como una responsabilidad federal. El gobierno federal se ve llamado a dirigir, catalizar y respaldar un esfuerzo colectivo con móviles locales, y lleva a cabo evaluaciones periódicas del progreso hacia esos objetivos.^{2,3} Este artículo presenta la situación actual en Puerto Rico respecto a los objetivos nacionales relacionados con el control de la hipertensión, o alta presión arterial, con la idea de presentar, tanto como de solicitar, estudios que examinen el tema en la isla.

Métodos

Las metas aquí reseñadas fueron traducidas por el autor y se citan, en comillas, tal como a parecen en el texto original en inglés.¹ Los estimados de incidencia mencionados como parte de la cita se refieren siempre a los Estados Unidos. Cada meta se rotuló "AA", "P", o "I" de acuerdo con los siguientes criterios: AA (aparentemente alcanzada) si la evidencia disponible indica que el estado de la enfermedado de la técnica de salud pública al momento actual en Puerto Rico concuerda con lo deseado para 1990; P (perseguida) si hay al momento un esfuerzo de recogida de datos respecto al problema y/o un programa establecido para el control de la enfermedad o prestación del servicio; I (indocumentada) si la información específica que estipula el objetivo no se conoce para Puerto Rico.

La "Muestra Básica", mencionada en la discusión de tres de los objetivos, es un estudio continuo (desde 1963) de la Oficina de Planificación, Evaluación y Desarrollo, del Departamento de Salud de Puerto Rico. Su propósito es recopilar datos sobre el estado de salud de la

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^{**}Estudiante de Cuarto Año, Clase de 1985, Escuela de Medicina de la Universidad de Puerto Rico

población, y los patrones de utilización de los servicios médico-hospitalarios. Consiste de entrevistas a una muestra representativa y sistemática de la población, derivada de la muestra seleccionada por el Negociado de Estadísticas del Trabajo del Departamento del Trabajo y Recursos Humanos de la población civil no institucionalizada de la isla.

Objetivos para 1990 o antes

*Mejoramiento del estado de salud

a. "Para 1990, por lo menos 60% de la población que se estime padezca de hipertensión indudable (160/95) debe haber logrado un control exitoso y a largo plazo de la hipertensión, es decir, una presión arterial en o por debajo de 140/90 por dos o más años consecutivos. (La tasa de control de hipertensión varía entre comunidades y estados, con valores desde 25 hasta 60%, según datos actuales.)"—I

No hay estudios que midan el porciento de hipertensos en Puerto Rico que hayan alcanzado un control de la hipertensión. Las entrevistas de la Muestra Básica de Salud en 1981 encontraron que el 8.1% de la población en general decía padecer de enfermedades hipertensivas. Las frecuencias con que se notificaron estas enfermedades en los distintos grupos de edad fueron las siguientes: 14-24 años: 0.3%; 25-44 años: 5.4%; 45-64 años: 23.0%; 65 años o más: 32.2% de los entrevistados.⁴ No es posible comparar estos datos con los de Estados Unidos, donde el 26% de la población tiene presión arterial sobre 140/90 y el 15% tiene presiones en o sobre 160/95. Los datos de la Muestra Básica se obtuvieron de entrevistas a una persona por familia y no de la toma de la presión arterial al individuo, de manera que reflejan solamente el porciento de la población que tiene hipertensión, según opinión de un conviviente, y no el porciento real que padece de esta condición silente. En un estudio de 1966, en que sí se tomaron presiones a los entrevistados, se encontraron presiones sobre 140/90 en 5% de la población, con una prevalencia máxima (13%) en la población de 60 años o mayor.⁵ Se han mencionado tasas de prevalencia de hipertensión sobre 30% en artículos posteriores, pero los datos surgen de muestras que no son representativas de toda la población insular (por ejemplo, una clínica de hipertensión en el Hospital de Veteranos de San Juan, y una clínica de cernimiento durante un día en un centro comercial).6, 7

*Reducción de factores de riesgo (Estos objetivos también están señalados en el área de Nutrición)

a. "Para 1990, la ingesta diaria promedio de sodio para adultos (medida por su excreción) debe ser reducida a un nivel menor de 3-6 gramos. (En 1979, se estimaban promedios de 4 a 10 gramos de sodio. Un gramo de sal provee aproximadamente 0.4 gramos de sodio.)"—I

A la población entrevistada para la Muestra Básica de enero a septiembre de 1975 se le preguntó sobre los alimentos consumidos dirariamente. A base de esas respuestas, la ingesta diaria promedio por persona para toda la isla era de 4.288 gramos de sodio.⁸ Este promedio abarca todas las edades, y no incluye el sodio añadido a

las comidas en su preparación y consumo en la mesa. La metodología usada en esta encuesta no es la que exige el objetivo, y es muy poco apropiada para medir verazmente el consumo de sodio. La ingesta promedio citada sólo puede tomarse como un valor mínimo, sin saber cuán cerca está del valor real.

c. "Para 1990, la prevalencia de obesidad significativa (120% del peso 'deseado') en la población adulta de EU debe reducirse al 10% de los hombres y 17% de las mujeres, sin causar perjuicio nutricional. (En 1971-74, 14% de los hombres adultos y 24% de las mujeres adultas pesaban más del 120% del peso 'deseado'.)"—I

La prevalencia de obesidad (120% del peso "standard") en la población puertorriqueña mayor de 18 años en 1966 era de 12% en los hombres y 28% en las mujeres.9 No hay estudios más recientes de la prevalencia de obesidad en la población general de la isla. En una muestra representativa de varones de 40 a 69 años de edad, examinados en 1965, se encontró una prevalencia de obesidad (peso relativo ≥120%) de 17% en los residentes de áreas rurales y 45% en los residentes de áreas urbanas. 10 Otro estudio más reciente utilizó la población entrevistada por la Muestra Básica de enero a septiembre de 1975 (como en el objetivo anterior, pero con visitas a los hogares que se llevaron a cabo de junio de 1975 a noviembre de 1976). Se encontró una prevalencia de obesidad (porciento de peso para estatura $\geq 120\%$) de 3.9% en niños y niñas de 1 a 6 años de edad.11 Las definiciones de obesidad en los tres estudios citados son muy similares, pero no lo suficientemente específicas como para asegurar que son idénticas.

*Mayor concientización pública y profesional

d. "Para 1990, por lo menos 50% de los adultos deben poder señalar los principales factores de riesgo para la cardiopatía coronaria y accidentes cerebrovasculares, que son los siguientes: hipertensión, fumar cigarrillos, niveles elevados de colesterol en sangre, y diabetes. (No hay datos de referencia disponibles.)"—I

De 1965 a 1982 miles de hombres puertorriqueños participaron en un estudio de factores relacionados con el desarrollo de cardiopatía coronaria. ^{12,13} Sin embargo, no existe ningún estudio que explore el porciento de adultos en Puerto Rico que puedan señalar los factores de riesgo para las condiciones mencionadas.

e. "Para 1990, por lo menos el 90% de los adultos deben poder señalar si su presión arterial actual es normal (menor de 140/90) o elevada, basándose en una medición obtenida en la más reciente visita a un profesional médico o dental, u otro personal entrenado en medir la presión arterial. (En 1971-74, 55% de las personas con hipertensión sobre 160/95 no estaban conscientes de su condición.)"—I

No hay estudios que señalan el porciento de adultos en Puerto Rico que pueden señalar si su presión arterial es normal o elevada.

*Mejoramiento en los servicios y la protección

f. "Para 1990, ningún área geopolítica de los Estados Unidos debe carecer de un programa público efectivo para identificar personas con hipertensión y para darle seguimiento a su tratamiento. (No hay datos de referencia disponibles.)"—I

No existe en la actualidad en la isla un programa público para identificar y darle seguimiento al tratamiento de los hipertensos. Existen programas aislados en las clínicas públicas donde se atienden los hipertensos ya identificados.

g. "Para 1985, al menos 50% de los alimentos procesados vendidos en los colmados deben estar rotulados para informar al consumidor el contenido de sodio y calorías, utilizando términos comprensible, estandarizados y cuantitativos. (En 1979, la rotulación para sodio era escasa; la prevalencia en el mercado de rotulación sobre calorías era cerca de 50%.)"—P

La mayoría de los alimentos procesados consumidos en Puerto Rico son importados de los Estados Unidos. Por lo tanto, la rotulación de estos productos depende de incentivos o legislación al respecto en el continente. Ya "Food and Drug Administration" ha establecido reglamentos que entrarán en vigor después de julio de 1986 y exigen a los productores presentar el contenido de sodio de los productos alimenticios que lleven etiquetas señalando su valor nutritivo. 14, 15 Al momento no hay legislación local respecto a señalar el contenido de sodio y calorías en las etiquetas de los alimentos procesados en Puerto Rico.

*Mejoramiento en los servicios de vigilancia y evaluación

h. "Para 1985, debe desarrollarse un sistema para la determinación de la incidencia de hipertensión, cardiopatía coronaria, fallo cardíaco congestivo, y apoplegía hemorrágica y obstructiva. Luego que la viabilidad del sistema sea demostrada, para 1990 la recogida de estos datos debe estar en funcionamiento."—I

No hay al presente un sistema en el Departamento de Salud para la determinación de la incidencia de las condiciones antes mencionadas.

i. "Para 1985, se debe desarrollar una metodología para evaluar las categorías de control de la hipertensión, y se debe completar un estudio nacional de referencia usando estas categorías. Se sugieren cinco categorías: (1) Paciente que desconoce su condición; (2) Consciente de su condición, pero sin tratamiento; (3) Consciente, en tratamiento, pero la hipertensión no está controlada; (4) Consciente, en tratamiento, controlado; (5) Consciente, vigilado sin terapia."—I

Ni en Puerto Rico ni en Estados Unidos se ha desarrollado una metodología como la que aquí se pide para evaluar las categorías de control de la hipertensión.³

Discusión

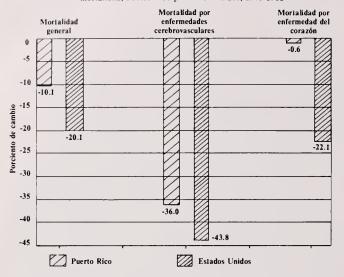
De los factores de riesgo para la cardiopatía coronaria ("coronary heart disease") y los accidentes cerebrosvasculares ("strokes"), la hipertensión es probablemente el más poderoso. Disminuir la prevalencia de la hipertensión en la población significa reducir el principal factor de riesgo para la primera y tercera causa de muerte en Puerto Rico (cardiopatía coronaria y accidentes cerebrovasculares, respectivamente). Un factor muy importante y susceptible a control, fumar tabaco, no se menciona aquí pues, por su importancia como uno de los

quince asuntos prioritarios en las metas nacionales de salud para 1990, se tratará por separado. De las nueve metas referentes al control de la hipertensión, sólo una está en vías de conseguirse en Puerto Rico: la que pide que se indique el contenido de sodio y calorías en la rotulación de los alimentos. Las otras ocho metas se refieren a condiciones de salud y actitudes en la población, sobre las cuales se ha recogido poca o ninguna información reciente. Los datos que hay en Puerto Rico sobre las enfermedades hipertensivas son estadísticas de mortalidad. Se extraen de la información contenida en los certificados de defunción y se tabulan como parte de las estadísticas vitales del país.

En vista de que los objetivos de salud para 1990 fueron redactados teniendo en mente las condiciones de salud de todo Estados Unidos, y este artículo pretende examinar el progreso hacia esos objetivos en Puerto Rico, es forzoso comparar los datos provenientes de ambos lugares. Puerto Rico tiene una tasa de mortalidad general mucho menor que la de Estados Unidos (658.2 vs. 852.0 muertes por 100,000 habitantes en 1982, sin ajustar por edad), por lo que la comparación de las tasas en un año dado sirve de muy poco. 16 17 Al comparar las tasas de mortalidad de ambos lugares hay que tomar en cuenta que la isla tiene una población más joven que la de Estados Unidos. Una comparación de las tendencias a largo plazo de las tasas ajustadas por edad (método directo, usando la población de Estados Unidos como referencia) es más útil, porque ajustar las tasas por edad cancela la diferencia de edades entre las poblaciones. De 1973 a 1982 la tasa general de mortalidad en Puerto Rico bajó un 10.1% (de 662.8 a 595.6 muertes por cien mil habitantes), mientras en Estados Unidos disminuyó el doble (20.1%, de 692.9 a 553.8, tasas ajustadas por edad) (ver figura). 16-19 De la misma forma, las tasas ajustadas por edad para mortalidad por enfermedades cerebrovasculares (ICDA 8 y 9: 430-438.9) han bajado en Puerto Rico un 36.0% (de 49.3 a 33.0 por cien mil habitantes) frente a un descenso mayor, de 43.8% en Estados Unidos (de 63.7 a 35.8 por cien mil habitantes).²⁰ En contraste, la tasa de mortalidad por enfermedades del corazón, que disminuyó 22.1% en Estados Unidos (244.4 a 190.5 muertes por cien mil habitantes), disminuyó sólo el 0.6% en Puerto Rico (159.2 a 158.2 muertes por cien mil habitantes).²² Este desfase entre las tendencias de mortalidad por enfermedades del corazón y enfermedades cerebrovasculares se notó también en Estados Unidos en las décadas de 1950 y 1960.²³ Por eso podría aducirse que estamos viendo en Puerto Rico tardíamente los mismos cambios que la industrialización causó en Estados Unidos en la primera mitad del siglo, o que es más difícil reducir las tasas de mortalidad de Puerto Rico, que en 1973 eran más bajas que las de Estados Unidos. Aunque así fuera, es claro que se necesitan programas efectivos para la educación de los profesionales de salud y la detección y seguimiento de los pacientes, porque al momento no tenemos ningún programa integral para combatir la hipertensión.

Las metas para 1990 hacen énfasis en la necesidad de conocer la frecuencia de las enfermedades hipertensivas en la población mientras vive, no después de su fallecimiento. De ahí el interés, no en la mortalidad, sino en la morbilidad causada por la hipertensión. Alcanzar en

Porciento de cambio en ciertas tasas de mortalidad, Puerto Rico y Estados Unidos, 1973-1982



Porciento de cambio en las tasas de mortalidad general, mortalidad por enfermedades cerebrovasculares, y mortalidad por enfermedades del corazón en Puerto Rico y Estados Unidos, 1973-1982. Información proveniente de las referencias 16 a 19.

Puerto Rico las metas nacionales referentes al control de la hipertensión no exige simplemente fortalecer unos programas existentes, sino crear sistemas de vigilancia y servicio radicalmente diferentes a los que hasta ahora se han utilizado.

Abstract: Of the nine national health goals for 1990 alluding to high blood pressure control, only one is being pursued in Puerto Rico, the labeling of foods to inform the consumer of sodium and caloric content. The other goals need to be developed from the very basic stages. The achievement of these objectives in Puerto Rico, as in other states, requires the cooperation of many governmental, academic and voluntary institutions.

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CHRYSLER NEW YORKER DEL '85 PRODUCTO DE LA NUEVA TECNOLOGIA CHRYSLER

Chrysler presenta la nueva tecnología automotriz en su más avanzado sedán de lujo, el New Yorker del '85.

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UNA VEZ LO CONDUZCA, NO VOLVERA A UN V-8 JAMAS.



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"Use los estimados EPA para comparación. Puede variar de acuerdo a las condiciones de la carretera o la condicion del vehículo.
"5 años ó 50,000 milias, lo primero que ocurra. Garantia limitada sobre el motor, el tren de fuerza y el tratamiento anti-corrosivo de la carrocena externa. Un deducible podrá ser requerido. Para más detalles, visite su distribuidor más cercano.

What can you do for hypertensives like Mary B?

Uncontrolled

Moderate hypertension (160/110 mmHg) with recent increases despite medication.

Forgetful

Misses appointments and frequently fails to follow instructions.

Overweight

At 73 largely sedentary... weight even more of a problem now.

Coexistent diabetes

On daily insulin after diet, exercise, and oral agents failed.

Patient description is a hypothetical composite based on clinical experience and evaluation of data

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Rely on one-tablet-a-day dosage and cardioselectivity.

"Real life" efficacy

Mary B represents 2,165 women over 70 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians!

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even Mary B's difficult age group?

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management?

Use in diabetes

Although beta blockers may mask tachycardia occurring with hypoglycemia, TENORMIN may be tried with caution in patients with diabetes mellitus, like Mary B, who require beta-blocker therapy. It does not augment insulin-induced hypoglycemia and does not delay recovery of blood glucose levels to the same degree as propranolol.³⁻⁶

*Cardioselectivity denotes a relative preference for β_1 receptors, located chiefly in cardiac tissue. This preference is not absolute

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁷ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy!



For Mary B...and virtually all your hypertensive patients

TENORMIN® (atendol)



ONE TABLET A DAY ENORM (atenolol)

For Mary B... and virtually all your hypertensive patients

TENORMIN® (atenolol)

A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN* (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2-hydroxy-3-[1-methylethyl) amino] pripoxy]- Atenolol (free base) has a molecular weight of 26.6 it is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCI (300 mg/ml at 25°C) and less soluble in chloroform (3 mg/ml at 25°C). INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used along a concompanity with bar antibyperdensive agents, natire (adv. with a

sion. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

sion. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type duretic.
CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than tirist degree, cardiogenic shock, and overt cardiac failure (see WARNINGS)
WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory
tunction in congestive heart failure, and beta blockade carries the potential hazard of further
depressing myocardial contractility and precipitating more severe failure. In hypertensive patients
who have congestive heart failure controlled by digitalis and duretics, TENORMIN should be
administered cautiously. Both digitalis and atenolol slow AV conduction
In Patlents Without a History of Cardiac Failure: Continued depression of the myocardium with
beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the tirst
sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a
diuretic and the response observed closely. It cardiac failure continues, despite adequate digitalization and diuretic. TENORMIN therapy should be withdrawn.
Ischemic Heart Disease: Following abruptic essation of therapy with certain beta-blocking agents
in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases,
myocardial infarction have been reported. Therefore, such patients should be cautioned against
interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris,
when discontinuation of TENORMIN is planned, the patient should be carefully observed and
should be advised to limit physical activity to a minimum. TENORMIN should be reinstated it withdrawal symptoms occur.
Fronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN
GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospasatic dis

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic

the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene. TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V).

Dlabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected TENORMIN does not potentiate insulin-induced hypoglycema and, unlike nonselective beta blockers, does not detay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

should be monitored closely PRECAUTONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Drug Interactions: Catecholarmine-depleting drugs (eg., reserpine) may have an additive effect when given with beta-blocking agents Patients treated with TENORMIN plus a catecholarmine depletor should therefore be closely observed for evidence of hypotension and/or marked brady-

cardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal

of clonidine. Carcinogenesis, Mutagenesis, Impairment of Fertillity: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding. Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration. Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended

human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg $_{\rm h}$ not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose,

respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a derelated increase in embryo/tetal resorptions in rats at doses equal to or greater than 50 mg/kg 25 or more times the maximum recommended human dose. Although similar effects were no in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12 5 times maximum recommended human dose. There are no adequate and well-controlled studies in nant women. TENORMIN should be used during pregnancy only if the potential benefit justifies adolested to the father.

potential risk to the fetus

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers received.

atenoiol.
Pediatric Use: Salety and effectiveness in children have not been established.
ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estwere derived from controlled studies in which adverse reactions were either volunteered by
patient (U.S. studies) or elicited (eg, by checklist—foreign studies). The reported frequency ocited adverse effects was higher for both TENOPMIN and placebo-treated patients than where these reactions were volunteered. Where frequency of adverse effects for TENORMIN and places is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects).

teered and elicited side effects)

U.S. STUDIES (% ATENOLOL-% PLACEBO):
CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotens (2%-1%), leg pain (0%-0.5%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR. dizziness (4%-1%), vertigo (2%-0.5%) light-headedness (1%-0%), tredness (0.6%-0.5%), tatigue (3%-1%), lethargy (1%-0%), drow: ness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)
GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)
RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)
TOTALS U.S. AND FOREIGN STUDIES:

RESPIRATORY (See WARNINGS), wheeziness (0%-0%), dyspnea (0.6%-1%) TOTALS U.S. AND FOREIGN STUDIES: CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotens (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR. dizziness (13%-6%), vertigo (2%-0.2 light-headedness (3%-0.7%), tredness (26%-13%), tatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL diarrhea (3%-2%), nausea (3%-1%), dyspnea (6%-4%)
MISCELLANEOUS There have been reports of skin rashes and for dry eyes associated withe use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cathe symptoms have cleared when treatment was withdrawn. Discontinuance of the drug shoube considered it any such reaction is not otherwise explicable. Patients should be closely motored tollowing cessation of therapy

POTENTIAL ADVERSE EFFECTS: in addition, a variety of adverse effects have been report with other beta-adrenergic blocking agents, and may be considered potential adverse effects and the considered potential adverse effe TENORMIN (atenolol).

TENOFMIN (atenoiol)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura
Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress
Central Nervous System: Reversible mental depression progressing to catatonia, visual distances, hallucinations, an acute reversible syndrome characterized by disorientation of timplace, short-term memory loss, emotional lability with slightly clouded sensorium, decreasiformace on neuropsychometrics
Gastrointestinat: Mesentenc arterial thrombosis, ischemic colitis
Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon
Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker pradhas not been reported with TENOFMIN during investigational use and foreign marketing expence. Furthermore, a number of patients who had previously demonstrated established pre-

eactions were transferred to TENORMIN therapy with subsequent resolution or quiescence

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific infom on emergency treatment of overdosage is available. The most common effects expected with dosage of a beta-argueregic blocking agent are bradycardia, congestive heart tailure, hypote breephosage and progressions.

dosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypote bronchospasm, and hypoglycemia In the case of overdosage, treatment with TENORMIN should be stopped and the patient cituity observed. TENORMIN can be removed from the general circulation by hemodialysis in a tion to gastric lavage, the following therapeutic measures are suggested it warranted Bradycardia: Atropine or another anticholinergic drug. Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker. Congestive Heart Failure: Conventional therapy Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or epinephrine may be useful in addition to atropine and digitalis. Bronchospasm: Arminophylline, isoproterenol, or atropine Hypoglycemia: Intravenous glucose.

Hypoglycemia: Intravenous glucose

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tal
day either alone or added to diuretic therapy. The full effect of this dose will usually be seen w
one to two weeks. It an optimal response is not achieved, the dosage should be increased to
TENORMIN 100 mg given as one tablet a day increasing the dosage beyond 100 mg a day unlikely to produce any further benefit.

unlikely to produce any furner benefit. TENORMIN may be used alone or concomitantly with other antihypertensive agents includ thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of seve impairment of renal function. No significant accumulation of TENORMIN occurs until creating clearance falls below 35 ml/min/1 73 m² (normal range is 100-150 ml/min/1.73 m²); therefore tollowing maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml/min/1 73 m²)	Atenoiol Elimination Halt-life (hrs)	Maxımum Dos
15-35	16-27	50 mg daily
<15	>27	50 mg every oth

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done un hospital supervision as marked talls in blood pressure can occur.

HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol): round, flat, uncoated, white tablets Stuart embossed on one side and NDC No 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 10 tablets and tall-dose packages of 10 tablets of 100 mg TENORMIN (atenolol): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 101 embossed on the other side are supplied in bottles tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose and calendar packages at controllet temperature.

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ESTUDIOS CLINICOS

Retinal Stimuli in Ocular Accommodation

Manuel N. Miranda, M.D.* Sixto García-Castiñeiras, M.D., Ph.D.

Abstract: The monocular amplitude of accommodation of 22 eyes from patients between 18 and 34 years of age were determined using first an illumination from a 40 watt and then from a 75 watt tungsten bulb. Amplitudes were also obtained using a green, red, and blue filters with the same bulbs.

The highest amplitudes were elicited by the polychromatic light primarily from the 75 watt bulb. In order of descending amplitude green light elicited more amplitude of accommodation than red, and red more than blue.

The results demonstrate that chromatic aberration, illumination, and contrast are the most important factors in eliciting retinal stimuli in ocular accommodation.

The stimuli for accommodation that have been more often mentioned are blurring, chromatic aberration and the awareness of proximity.

A blurred image seems to be the stronger retinal stimuli, but the clear image must be formed behind the retina in order to elicit accommodation. It is well known that in hypermetropia and when the eyes view near objects closer than their far point, accommodation occurs. In these situations a blurred image is formed in the retina. When accommodation occurs the rays of light crossing the retina must be convergent. What is the mechanism that informs the eye about the vergence of rays crossing the retina in order to bring about accommodation?

The retina can send to the brain only two types of information, differences in the amount of illumination and differences in color.

It has been suggested that a possible mechanism of how the brain learns the nature of the necessary adjustments for accommodation, might be found from a consideration of the chromatic aberration of the eye. Thus white light, through chromatic aberration, forms an image in the retina with a blue center surrounded by a red fringe in hypermetropia and in an emmetropic eye adapted for near, while in myopia and in emmetropia it will have a red center surrounded by a blue fringe. It is possible that by this means the brain would know the nature of the light

vergence at the retina. If this is true, only polychromatic light could stimulate accommodation. Fincham, one of the investigators who have studied more extensively the subject of retinal stimuli in accommodation, tested patients with white and monochromatic sodium light (589 nm). He found that all subjects with white light actively accommodated, but with monochromatic light the response was different, approximately one third of the subjects did not accommodated at all, one third had a partial reaction and the other third reacted as well as with white light. Fichman concluded that chromatic aberration offered only a partial explanation to accommodation.

In order to investigate further the importance of chromatic and illumination factors, we decided to carry out experiments using a white light of varying intensity and three filters, green, red, and blue, to produce monochromatic light.

Method

The monocular amplitude of accommodation of 22 eyes from patients between 18 and 35 years of age were determined using first an illumination from a 40 watt and then from a 75 watt tungsten bulb located 40 cm. behind and above a reading chart. Amplitudes were also obtained using a green, red and blue filters with illumination of 6.25 foot candles to the reading chart and to the tested eye. The eye received through the green filter and red filter 3.5 foot candles and only 3.0 through the blue filter. The 75 watt bulb provided an illumination of 7 foot candles to the reading chart and to the eye behind the refractor. The eye received 4.0 foot candles through the green and red filter and only 3.5 through the blue filter.

Eyes selected did not present any pathology, had 20/20 distance vision and did not had ametropias of more than 1 diopter.

The patient was given an exact distance cycloplegic refraction using a 1% cyclopentolate solution. The amplitudes of accommodation were measured at least one week later.

The amplitude of accommodation was measured with a near visual acuity chart using type with a letter height of 0.485 mm., printed black on non-glossy white background and located at 33.3 cm. from the corneas to correspond to a visual acuity of 20/20 and a required accommodation of 3.00 D. The distance correction, carefully centered, was placed in a refractor 14 mm. from

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Results

			Kes	uits		
	cular Amplitude of Accommoda					
Age	Patient 1	OD	os		OD	os
20	40 watt tungsten bulb	8.00	8.50	75 w. tungsten bulb	9.00	9.00
	Green filter	7.50	8.00	Green filter	8.75	8.75
	Red filter Blue filter	5.00	5.25	Red filter	5.75	7.50
		3.25	3.25	Blue filter	5.25	5.00
	Patient 2					
19	40 watt tungsten bulb Green filter	12.00	12.50	75 w. tungsten bulb Green filter	12.25	12.50 11.00
	Red filter	7.50 4.00	7.25 4.00	Red filter	10.50 6.50	4.00
	Blue filter	J ₃	3.00	Blue filter	4.00	3.75
	Patient 3	3,	5.00	Bide inter	4.00	3.73
2.4		7.50	7.50	75	0.75	= =0
24	40 watt tungsten bulb	7.50	7.50 5.50	75 w. tungsten bulb Green filter	8.75	7.50
	Green filter	7.50	5.00	Red filter	8.75	6.75
	Red filter Blue filter	6.00 J ₃	J_7	Blue filter	6.00 3.25	5.00
		J ₃	J ₇	Dide filler	3.23	J_3
	Patient 4					
19	40 watt tungsten bulb	6.50	5.75	75 w. tungsten bulb	8.00	9.50
	Green filter	6.00	5.00	Green filter	6.25	7.25
	Red filter	4.25	3.25	Red filter	6.25	6.00
	Blue filter	J_3	3.25	Blue filter	3.75	5.25
	Patient 5					
35	40 watt tungsten bulb	4.75	4.75	75 w. tungsten bulb	5.00	5.50
	Green filter	4.75	4.75	Green filter	4.75	5.25
	Red filter	3.75	3.75	Red filter	4.50	4.00
	Blue filter	J_3	3.25	Blue filter	3.00	3.00
	Patient 6					
28	40 watt tungsten bulb	6.75	6.25	75 w. tungsten bulb	7.25	7.50
	Green filter	6.00	6.25	Green filter	7.00	7.25
	Red filter	4.25	5.25	Red filter	6.25	6.25
	Blue filter	J_3	J_3	Blue filter	J_3	J,
	Patient 7					
18	40 watt tungsten bulb	7.50	7.50	75 w. tungsten bulb	7.75	7.75
	Green filter	4.50	7.00	Green filter	6.50	7.50
	Red filter	4.50	4.00	Red filter	4.50	5.00
	Blue filter	J_2	J_2	Blue filter	J_2	J_2
	Patient 8					
27	40 watt tungsten bulb	7.00	6.75	75 w. tungsten bulb	8.50	9.00
	Green filter	7.00	6.75	Green filter	7.50	8.25
	Red filter	6.25	6.00	Red filter	6.75	7.50
	Blue filter	J_2	J_3	Blue filter	6.75	7.25
	Patient 9					
27	40 watt tungsten bulb	8.50	8.50	75 w. tungsten bulb	8.50	8.50
	Green filter	8.00	8.00	Green filter	8.50	8.50
	Red filter	6.50	7.00	Red filter	6.25	7.00
	Blue filter	\mathbf{J}_{\imath}	J_2	Blue filter	\mathbf{J}_2	J_2
	Patient 10					
28	40 watt tungsten bulb	6.00	5.75	75 w. tungsten bulb	6.75	6.25
	Green filter	5.50	5.50	Green filter	6.00	5.75
	Red filter	3.50	3.75	Red filter	3.75	4.25
	Blue filter	4.00	4.00	Blue filter	4.75	4.50
	Patient 11					
28	40 watt tungsten bulb	8.00	8.25	75 w. tungsten bulb	8.25	8.25
	Green filter	8.00	8.25	Green filter	8.00	8.25
	Red filter	6.00	5.50	Red filter	5.00	6.00
	Blue filter	\mathbf{J}_2	\mathbf{J}_{i}	Blue filter	\mathbf{J}_{2}	3.00

The highest amplitudes of accommodation were elicited by the polycromatic light from the tungsten lamps, primarely, from the 75 watt one. In order of descending amplitude the green filter elicited more A.A. than the red one and this in turn elicited more A.A. than the blue one.

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the cornea. Then the patient was asked to read loudly the paragraph of the smallest letters corresponding to a visual acuity of 20/20. Minus spheres were added first in 0.50 D step and later in 0.25 D until the test could no longer be read. The amplitude of accommodation was 3.00 D plus the number of minus diopters added. The test was repeated using a green filter with a maximum transmission of 525 nm, a red filter with a maximum transmission of 700 nm, and a blue filter with transmission from 310 to 475 nm placed in close contact to a refractor in order to prevent white light refleted from the near acuity chart from going into the eye.

Discussion

The chromatic aberration theory as the stimulus for accommodation would provide a relatively simple and straightforward mechanism for the eye to detect the convergence of the light rays reaching the retina. Thus, a peripheral ring of red would be formed only when a blurred image is formed behind the retina. This theory implies that monochromatic light should be unable to elicit accommodation. However, the results of our experiments demonstrate that monochromatic light is capable of eliciting accommodation although to a lesser extent than polychromatic light. Green light was almost as effective as white polychromatic light. Red light followed in effectivity. Blue light was the least effective stimulus for accommodation.

How, then, a defocus of the image at the retina produced by convergent light is converted into a stimulus for accommodation?

Several other theories have been advanced, one of which may be supported by our results.² We realized early in this work that the level of illumination was an important factor in deciding the amplitude of accommodation. Thus, the average amplitude of accommodation obtained in our subjects increased 10% for white light, 16% for green and red lights and 153% for blue light when a 75 watt was used instead of a 40 watt lamp as the source of illumination.

We believe, therefore that the level of illumination, possibly acting through contrast effects, may play an important role in eliciting accommodation. One theory that considers these effects has been advanced by Alpern.³ This author considers that the ciliary muscle system moves in the direction that produces the highest contrast of the image in the retina. The system is continuously oscillating, so that when defocus occurs, the favoured response would be that of increasing contrast. Accommodation would only occur then when the light rays are converging on and the image is formed behind the retina.

Other aspects of our results deserve comment. The pattern of effectivity of different wavelenghts of light in eliciting accommodation suggests that the foveal cones are the receptors of the stimuli. Thus, green light is almost as effective as polychromatic light, and blue and red light are less effective. This matches the wavelength discrimination curve of the eye, the light detection thresholds of the fovea and the photopic luminous efficiency of the cones. Particularly ineffective for accommodation is blue

light and this could be due to the relative lack of blue cones in the central fovea.

When accommodation in our subjects was studied as a function of age, it was found that for polychromatic light it linearly decreased with age. The slope of the line obtained corresponds to that described before for individuals below 36 y/o in a previous study of one of the authors. However, this age-dependence of the amplitude of accommodation was progressively lost when the latter was measured with monochromatic lights. This effect increased in going from green to red to blue lights. We do not have at the present time an explanation for this intriguing, previously unreported finding.

Finally, although it has been stated that chromatism is essential in eliciting the accommodation reflex the following case report indicates that this may not be so. We examined a 21 y/o female patient with achromatopsia (total color blindness). Her right eye was exotropic and even though she had a corrected vision of 20/300 with a +3.75 -2.50 X10 lens, accommodation could not be measured. However, in the left eye, in spite of having a 20/200 vision with a lens of +5.25 -2.50 X165, it could be measured. She showed a monocular amplitude of accommodation of 6.00 D for polychromatic light from both the 40 watt and 75 watt bulbs. Furthermore, blue, as well as green light elicited the same degree of accommodation as polychromatic light, while red light did not elicited any accommodation of all, suggesting that the photoreceptors involved in the reflex are qualitatively different than in a normal person. Achromatopsic patients can only perceive white, black, and grey colors, enough in this patient to form a blurred image with relatively good contrast.

In conclusion, we can state that chromatic aberration, illumination, contrast and a blurred image at the retina with the clear image falling behind the retina are the most important factors in eliciting retinal stimuli in ocular accommodation.

Resumen: Se determinó la amplitud monocular de acomodación en 22 ojos de pacientes entre los 18 y 34 años de edad usando iluminación de bombillas de tungsteno de 40 y 75 vatios. También se obtuvieron amplitudes usando filtros verde, rojo y azul.

La luz policromática, proveniente especialmente de la bombilla de 75 vatios, produjo las amplitudes de acomodación mayores. En orden descendente la luz verde estimuló un grado mayor de amplitud que la roja y la roja más que la azul.

Los resultados del estudio demostraron que la aberración cromática, la iluminación y el contraste son los factores más importantes en estimular retinalmente la acomodación ocular.

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The Use of C-Reactive Protein in Spinal Fluid of Pediatric Patients for the Differentiation of Bacterial from Nonbacterial Meningitis

Emilio Betancourt Monzón, M.D.* Ramón G. Montes, M.D.**

Abstract: The use of the latex agglutination method to detect C-reactive protein in cerebrospinal fluid was considered a reliable tool by a group in Baltimore, Maryland (Corrall et al). It was utilized in the differentiation of bacterial from nonbacterial meningitis in pediatric patients.

Thirty three pediatric patients with the diagnosis of meningitis were studied. The diagnosis was established by the presence of pleocytosis and/or a positive gram stain in cerebrospinal fluid (CSF). The cases were divided in two age groups; 0-7 weeks and from 7 weeks to 18 years. Routine spinal fluid analysis and C-reactive protein (CRP) were performed in all patients.

In both groups CRP was more sensitive and produced less false negative results than other CSF parameters measured. The spinal fluid findings in 3 cases were consistent with a viral meningitis. These 3 cases had a positive CRP result. All were started on antibiotic therapy due to this (+) CRP result. Blood cultures revealed Hemophilus influenzae type B in two of them and group B streptococcus in the other. Even though our sample population was small, our findings seem to be consistent with the results of the group from Maryland.

The presence of CRP in CSF is highly suggestive of a CNS inflammation secondary to a bacterial process.

The concept of C-reactive protein was initially utilized by Francis & Tillet in 1930.² They found that sera from patients with pneumococcal pneumonia precipitated a substance called somatic C-polysaccharide. This precipitation reaction did not occur in the sera of normal patients or in those with viral illness.

It was not until 1941 when the C-polysaccharide was shown to be a protein, and in that same year it was designated as C-reactive protein.

Recently, the presence of C-reactive protein in spinal fluid of patients with meningitis has been used as a diagnostic tool, attempting to distinguish a bacterial from a non-bacterial form of this disease. There has been extensive investigations with other laboratory parameters, but the results have been variable concerning the differentiation of septic from aseptic meningeal inflammation

or infection. Some of the parameters studied have been: cerebrospinal fluid determination of glucose, protein, lactate, anion gap, enzymes, counter immune electrophoresis for identification of common pathogenic bacterial antigens, nitroblue tetrazolium dye test and the lymulus lysate test.

For more than 50 years clinicians have searched for a rapid and reliable test that could differentiate central nervous system infection caused by viral or by bacterial agents.

Errors and associates' described a rapid microenzy-matic method to measure cerebrospinal fluid lactate. They claimed that this method was effective in distinguishing bacterial from non bacterial meningitis. It was possible to document that a patient with bacterial meningitis had significantly higher cerebrospinal fluid lactic acid levels than patients with viral meningitis. One of the problems found by other investigators was that false positives did occur in significant statistical numbers. Corral published results concerning 56 patients with meningitis. They found that C-reactive protein was detected in 100% of patients with bacterial proven meningitis. There was only one neonate in this study.

Surprisingly enough, Alistair and associates found in their study that C-reactive protein levels in spinal fluid were not a reliable parameter for distinguishing septic from aseptic meningitis in neonates.⁵ Another study by Clark and Cost showed that C-reactive protein levels in serum were significantly increased and should be taken into account when trying to differentiate a viral from a non-viral agent as the cause of meningitis.⁶

Due to this general controversy we decided to study our own patient population at the Caguas Regional Hospital. We wanted to determine the value of this laboratory test (C-reactive protein in CSF) as a clinical tool in the differentiation of bacterial from non bacterial meningitis.

Material and Methods

Cases enrolled in this study were those with a diagnosis of meningitis. Our patient population consisted of 33 children which were divided into two major groups. The first group was from 0-6 weeks of age, and the second group from 7 weeks to 18 years of age.

The study extended from January 1, 1982 to August 1, 1983. The cerebrospinal fluid was obtained from infants and children with signs of meningeal irritation. Meningi-

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tis was defined as pleocytosis: 30 or more WBC/mm³ in cerebrospinal fluid of the neonate, and 10 or more WBC/mm³ in patients beyond this age period. The cerebrospinal fluid was collected in 4 sterile tubes. It was sent to the laboratory and analyzed within the next 1-2 hours. Processing was undertaken at the hospital clinical laboratory for determination of cells, differential count, total number of leukocytes, and glucose and protein concentration. One sterile tube was stored at 20°C for Creactive protein testing. This was done only if the cerebrospinal fluid was positive for meningitis. A gram stain of the material was done inmediately. There were instances when the cerebrospinal fluid was stored at 35° C, for 8 to 12 hours while appropriate culturing on microbiologic media for bacterial isolation was done. In general, this material was cultured in approximately 2-4 hours after being received at the laboratory. No virology analysis was performed.

C-reactive protein determination was done by a qualitative method utilizing latex agglutination to detect the presence of C-reactive protein. Thirty microliters each of undiluted cerebrospinal fluid, positive and negative control sera were placed in separate wells on a glass slide. Thirty microliters of anti C-reactive protein antibody coated latex particles were added to each well. The slide was manually agitated at room temperature for 4 minutes, then examined with the naked eye.

A positive slide test consisted of a similar agglutination when compared with the positive control serum. A negative slide test showed a smooth or slightly granular homogenous material with no visible agglutination, as in the negative control serum.

Results

Table No. I shows the results of a total of 14 cases in the 0-6 weeks age group. It depicts some parameters encountered in the cerebrospinal fluid and blood of these patients. In this group there was one CSF culture proven meningitis. It ocurred in a 21 days old patient. The microorganism obtained in blood and cerebrospinal fluid was a group B streptococcus. Two other cases

demonstrated positive gram stain, but microoganisms were not recovered in the CSF. In all cases with a positive gram stain and in the case of a positive CSF culture, the Creactive protein was positive.

Cases number 2, 9, 10, 11 and 13 had a negative C-reactive protein test, gram stain and cerebrospinal fluid culture. In these cases antibiotherapy was witheld or discontinued and the patients were observed.

None of these patients showed complications. All CSF and blood cultures were confirmed to be negative. The average stay at the hospital for these patients was 7 days after which they were discharged. Case No. 8 had a negative C-reactive protein test, gram stain, and spinal fluid culture but nevertheless was started on antibiotherapy. The patient received 21 days of treatment, with a 23 day stay at our unit. In contrast, cases 1, 3, 5 and 7 had negative gram stain and spinal culture, but presented a positive C-reactive protein in cerebrospinal fluid. These received antibiotics for 21 days. All presented very low glucose values in the cerebrospinal fluid (40 mg/dl) except for case number 1, who had a CSF content of 47 mg/dl.

Table No. II demonstrates the results obtained in the nineteen patients of the 7 weeks to 18 years age group. Three cases had culture-proven meningitis and four cases had positive gram stain, only two of which presented positive spinal cultures.

Cases number 2, 3, 7, 13, 18 and 19 were not treated with antibiotics. All cases had negative gram stain, CRP, blood and CSF cultures. Average hospital stay for observation and confirmation of negative cultures was 5 days.

In cases number 8, 9, and 11, the gram stain and spinal fluid culture were negative. C-reactive protein was positive in all three of them in spite of negative CSF culture. Antibiotherapy was given to all three patients. These blood cultures later showed growth for *Hemophilus influenzae* type B, group B streptococcus, and Hemophilus type B respectively. All three had more than 1,000 RBC in spinal fluid at the time of the diagnostic lumbar puncture.

TABLE I

	Spinal Fluid Analysis Age: 0-6 Weeks												
No.	Age.	RBC*	WBC*	%PMN*	GRAM*	Sp/c*	CRP*	Glucose	Protein	BS*	B/C*	AB's*	Comments
1	21 days	294	720	3%	Neg.	Neg.	Pos.	47	72	80	Neg.	A+G/21	DH-25 days
2	40 days	84	154	20%	Neg.	Neg.	Neg.	27	42	70	Neg.	A+G-4	DH- 7 days
3	6 wks.	4	514	60%	Neg.	Neg.	Pos.	23	60	120	Neg.	A+G-21	DH-24 days
4	4 wks.	1	385	9%	Gr(-)bacilli	Neg.	Pos.	46	70	90	Neg.	A+G-21	DH-24 days
5	24 hrs.	217	70	71%	Neg.	Neg.	Pos.	14	210	45	Neg.	A+G CL+AK	Severe hydrocephalus PTAGA Transferred to CH
6	21 days	77	864	70%	Gi (+) cocci	GBS	Pos.	4.9	295	160	GBS	A+G-21	DH-25 days
7	4 wks.	7	725	96%	Neg.	Neg.	Pos.	15	113	100	Neg.	A+G-21	DH-23 days
8	6 wks.	1.242	747	95%	Neg.	Neg.	Neg.	41	76	80	Neg.	A+G-21	DH-23 days
9	6 wks.	1	209	97%	Neg.	Neg.	Neg.	44	72	140	Neg.	None	DH- 8 days
10	29 days	157	263	40%	Neg.	Neg.	Neg.	рĢ	68	70	Neg.	None	DH- 3 days
- 11	4 wks.	3,340	44	50%	Neg.	Neg.	Neg.	34	65	100	Neg.	None	DH- 6 days
12	4 wks.	140	283	100%	Gr(-)bacilli	Neg.	Pos.	35	105	166	Neg.	A+G-21	DH-22 days
13	26 days	16,992	63	60%	Neg.	Neg.	Neg.	29	86	70	Neg.	None	DH- 5 days
14	22 days	171	233	60%	Neg.	Neg.	Pos.	28	68	80	Neg.	A±G-18 days	DH-19 days

TABLE 11

			Spinal Fluid Analysis /7 Weeks — 18 Years										
No.	Age.	RBC	WBC	%PMN	GRAM	Sp/c	CRP	Glucose	Protein	BS	B/C	AB's	Comments
,	2 mo.	0	215	61%	Neg.	Neg.	Neg.	19	28	100	Neg.	A+C-10 days	DH- 8 days
1		6	121	35%	Neg.	Neg.	Neg.	53	47	65	Neg.	None	DH- 5 days
2	2 mo. 2 mo.	147	331	39%	Neg.	Neg.	Neg.	35	74	100	Neg.	None	DH- 4 days
3		288	6,480	100%	Neg.	Neg.	Pos.	18	142	80	Neg.	P+C-10 days	DH-11 days
4	14 yrs.	348	221	69%	Gr(-)bacilli	H.inf.B	Pos	4.6	80	57	Neg.	A+C-10 days	DH- 9 days
5	2 yrs.	340 6	126	1%	Neg.	Neg.	Pos.	39	78	103	Neg.	A+C-10 days	DH-11 days
6	9 yrs.	390	120	33%	Neg.	Neg.	Neg.	36	18	80	Neg.	None	DH- 4 days
7	3 mo.		485	8 5 %	Neg.	Neg.	Pos.	0	93	75	H.inf.B	A+C-10 days	DH-15 days
8	3 mo.	1,260	17	41%	Neg.	Neg.	Pos.	44	38	210	GBS	A+C-10 days	DH- 9 days
9	3 mo.	5,670		96%	Gr(-)	H.inf.B	Pos.	40	194	130	H.inf.B	A+C-14 days	DH-20 days
10	5 mo.	122	1,490	90%	Cocobacilli	11.1111.15	1 00.					•	
			330	85%	Neg.	Neg.	Pos.	29	169	100	H.inf.B.	A+C-12 days	DH-13 days
11	2 mo.	1,400	328	40%	Neg.	Neg.	Pos.	29	92	90	Neg.	A+C-10 days	DH-13 days
12	3 mo.	60	55		_	Neg.	Neg.	44	27	90	Neg.	None	DH- 5 days
13	3 m o.	11	280	38%	Neg.	H.Inf.B	Pos.	10	80	46	Neg.	A+C-10 days	DH-11 days
14	2 yrs.	348	220	43%	Neg.	Neg.	Neg.	84	65	100	Neg.	A+C-10 days	DH-11 days
15	3 mo.	90	55	100%	Neg.	Neg.	Pos.	57	17	60	Neg.	A+C-10 days	DH-12 days
16	7 m o.	917	2	0%	Gr(-)bacilli	Neg.	1 03.	3,	• ′				persistent neutropenia
17	6 mo.	70	156	40%	Gr(-)	Neg.	Neg.	66	78	100	Neg.	A+CL-10 days	DH-11 days
1 /	o mo.	70			Diplococci								****
18	4 mo.	4	305	85%	Neg.	Neg.	Neg.	61	33	74	Neg.	A+C-1 day	DH- 4 days
18	6 mo.	8	584	54%	Neg.	Neg.	Neg.	44	130	95	Neg.	None	DH- 5 days

Case No. 17 presented two isolated images in the gram stain that were considered positive and compatible with a gram negative diplococci. C-reactive protein was negative (repeated twice for confirmation) along with a negative spinal culture and a normal CSF glucose with respect to blood sugar. This patient's twin sister (case No. 19) was admitted one day later with similar symptoms. The CSF was negative for C-reactive protein, gram stain and culture. The diagnosis of aseptic meningitis was done and the patient discharged 4 days later.

Case No. 16 deserved special attention. This 7 month old patient did not have spinal fluid pleocytosis but presented positive C-reactive protein test as well as a positive gram stain. He received antibiotherapy and was treated as a case of bacterial meningitis. All CSF cultures were negative. The patient's twin brother died one week previous to the admission secondary to a septic shock. Persistent neutropenia was the hallmark in this case along with normal serum inmunoglobulins and T cell population.

Tables number III, IV, V and VI present biostatistical values for C-reactive protein, glucose, gram stain and total WBC. All these parameters were studied as variables with respect to a positive spinal fluid culture and/or gram stain used as a 100% specific common denominator.

In Table No. III, C-reactive protein showed 100% sensitivity in the zero to 6 weeks age group, in contrast with lesser sensitivity rates for other parameters studied. False negative results were high for glucose and total WBC's in the cerebrospinal fluid. C-reactive protein had a 0% rate of false negatives. Sensitivity values were also very high for gram stain as a single variable. C-reactive protein presented an approximate 55% specificity in this statistical analysis, lower only to the value for WBC.

In the 7 weeks to 18 years age group, the sensitivity of C-reactive protein test fell to 90% and the false negative percentage increased to 10%. When the other variables

studied (gram stain, total WBC count, glucose) were compared as a group to the C-reactive protein it was demonstrated that they had a lower sensitivity rate and a greater rate of false negatives. Specificity was in the range of 50 and 90% for the gram stain and the total WBC's respectively when they were studied as independent variables.

TABLE III

Biostatistical Values of CSF Studies

In Relationship with CRP									
Age	Specificity	False Positive	False Negative	Sensitivity					
Zero - 6 wks	55%	45%	None	100%					
7 wks - 18 yrs	70%*	30%**	10%	90%					

* If positive B/cultures of cases 8, 9, 11 were considered, specifity would be 90%. All had more than 1,000 RBC in CSF.

** If B/cultures of cases 8, 9, 11 would be considered False Positive,% would be 10%

TABLE IV

Biostatistical Values of CSF Studies In Relation to Gram Stain Age Specificity False False Sensitivity Positive Negative Zero - 6 wks 33% 66% 0% 100%						
Age	Specificity			Sensitivity		
Zero - 6 wks	33%	66%	0%	100%		
7 wks - 18 yrs	50%	50%	12%	88*		

^{*}If positive B/cultures of cases 8, 9 and 11 were considered, sensitivity would fall to 69%.

TABLE V

Biostatistical	Va	lues	of	CSF	St	udies
In Relation	to	Glu	ICOS	e Le	vel	of
	40	mg/	/dl			

Age	Specificity	False Positive	False Negative	Sensitivity
Zero - 6 wks	22%	78%	66%	33%
7 wks - 18 yrs	30%	70%	60%	40%

Glucose level was chosen to be significant at less than 40 mg/dl due to previous studies and according to normal values with regard to age.

TABLE VI

Biostatistical Values of CSF Studies In Relation to WBC Level of 500* Cells/mm³

Age	Specificity	False Positive	False Negative	Sensitivity
Zero - 6 wks	64%	36%	67%	33%
7 wks - 18 yrs	90%	10%	80%	20%

Level of 500 Cells/mm³ was chosen as in previous studies.

Discussion

C-reactive protein was first measured in spinal fluid by Claussen et al in Denmark in 1962.¹⁰ It was not until 1981 when a prospective study was undertaken using C-reactive protein in cerebrospinal fluid. For the first time it was used as a screening method to detect central nervous system inflammation caused by a bacterial agent.¹

The study done by Corral, et al in Baltimore, Maryland, showed that the presence of C-reactive protein in cerebrospinal fluid (by the latex agglutination method) was indicative of a bacterial meningitis, with a 100% sensitivity and a 94% specifity. These findings were different from those later encountered by Alistair, Phillip and Baker. Their patient population consisted exclusively of neonates and they used the laser beam nephelometry method to detect C-reactive protein. They found that the presence of C-reactive protein in the cerebrospinal fluid of neonates did not correlate with the presence of bacteria. They felt that the cause of these findings was secondary to the inability of this age group to produce or initiate an appropriate antibody response.⁵ This phenomenon has been well documented for neonatal group B streptococcal infection in which patients fail to initiate an antibody response.5, 7 Consideration was also given to the possibility that Creactive protein was consumed more rapidly than it was produced. Although studies have shown that C-reactive protein is involved in the defense mechanism, it is unclear whether protection^{8, 9} requires an excess of the protein or whether depletion may occur as a result of consumption of the protein.5

Another important finding in this study was a good correlation between laser nephelometry and latex agglutination in the determination of spinal fluid C-reactive

protein.

In our study, we confirmed the findings of Corral et al which indicated that the presence of C-reactive protein in cerebrospinal fluid was more reliable than the gram stain, glucose, or total WBC's count in determining the presence of a bacterial meningitis.

In contrast with the study of Alistair⁵ it was precisely in the age group of 0-6 weeks of age where our sensitivity value for C-reactive protein was the highest, being 100%, although only one case had group B streptococcal meningitis. Our findings in this age group supplement Corral's study and are similar to his general results.

The low sensitivity values for the other parameters measured (glucose, gram stain, total WBC's). It also compare favorably with the findings of previous studies.

Clarke and Cost found that there was a considerable overlapping of values for those parameters when they were used to distinguish a viral from a bacterial meningitis.⁶ There was no overlapping with the Creactive protein determination in serum.

A critical finding in our study was that the presence of C-reactive protein in spinal fluid was the lone early indicator of bacterial infection in some cases. This situation clearly demonstrates how sensitive and probably life-saving C-reactive protein testing proved to be in these previously discussed patients. The lone false negative C-reactive protein result in our study raised doubts as to the accuracy of the gram stain procedure in that case, in view of the previously discussed clinical situation.

It seems appropriate to conclude that C-reactive protein detected by a latex slide test seems to be a helpful tool in the differentiation of bacterial from a non bacterial CNS inflammation at the bedside.

With the possible exception of neonates with Group B streptococcal infection, in which further studies are warranted, the determination of C-reactive protein in the spinal fluid is superior to traditional clinical parameters, especially in equivocal cases.

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Correlación entre Niveles Séricos de Amitriptylina y la Escala Hamilton de Depresión Usando Cromatografía Líquida de Alta Presión

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Resumen: Este estudio fue diseñado con el fin de desarrollar una metodología para medir los niveles de amitriptylina (Elavil) en la sangre mediante el uso de la cromatografía líquida de alta presión (HPLC) y determinar si existe una relación entre los niveles séricos de amitriptylina, las puntuaciones en la escala Hamilton de depresión (EHD) y sus siete factores. El estudio se realizó en siete pacientes. Estos fueron al hospitalizados y cumplían con los criterios de depresión mayor de acuerdo al Manual Estadístico y Diagnóstico de Trastornos Mentales (DSM-III). Los pacientes se trataron con amitriptylina en dosis orales de 75-200 mg/día. Encontramos que el método podía detectar concentraciones de 5 ng/ml. En los análisis gráficos del estudio observamos unos patrones curvilíneos que sugieren la existencia de una relación entre los niveles de amitriptylina y la EHD. Sin embargo, los resultados de este estudio piloto no son estadísticamente significativos debido al número pequeño de pacientes.

En los últimos años se han desarrollado nuevas técnicas para medir los niveles séricos de varios agentes psicotrópicos. Múltiples investigaciones con algunos antidepresivos han mostrado correlaciones entre los niveles de estos en plasma y la respuesta terapéutica.^{1, 2, 3, 4} No obtante aún se requiere más investigación para aclarar la relación entre los niveles séricos y aquellos subcomponentes clínicos que cambian con el tratamiento.

Los niveles de nortriptylina en la sangre fueron medidos por Asberg et al⁵ quienes reportaron en el año 1971 el concepto de "Ventana Terapéutica", también conocida como "correlación curvilínea" para este antidepresivo. En esta correlación ellos encontraron dos márgenes, uno inferior, de 50 ng/ml y otro superior, de

140 ng/ml. Entre estos márgenes estaban las posibles concentraciones en plasma del antidepresivo con las que se produjo una máxima eficiencia terapéutica. En investigaciones subsiguientes se obtuvieron resultados similares⁶⁻¹² fortaleciendo la evidencia a favor de una ventana terapéutica para la nortriptylina. Sin embargo, en otras investigaciones¹³⁻¹⁶ no se ha encontrado tal correlación debido probablemente a factores relacionados con la metodología para medir los niveles del antidepresivo en la sangre o a factores independientes de la muestra.¹

Los resultados de los estudios con amitriptylina* son aún más controversiales. Varios investigadores han reportado una correlación positiva entre la concentración de amitriptylina en plasma y la respuesta terapéutica.^{17, 18, 19} Comenzando con niveles de 120 ng/ml, la mejoría clínica va en aumento mientras sube la concentración en plasma hasta aproximadamente 250 ng/ml. Existen otros estudios donde se ha encontrado una ventana terapéutica de 80-220 ng/ml pero estos incluyen amitriptylina y su metabolito nortriptylina en el suero.²⁰⁻²² Finalmente, en otras investigaciones no se encuentra relación alguna entre la respuesta clínica y los niveles en plasma, ya sea de concentraciones individuales de amitriptylina o de éstas sumadas con nortriptilina.23, 24 Esta inconsistencia de los resultados de las investigaciones con amitriptylina puede deberse a un sinnúmero de factores: 1) No está claro ni se debe medir cada compuesto independientemente o sumar las concentraciones de ambos; 2) el número de estudios realizados es pequeño lo que no permite una buena comparación entre ellos; 3) algunos estudios presentan problemas metodológicos tales como diferencias en el manejo de especímenes, lo que impide una comparación directa de los resultados de las distintas investigaciones.

Se han publicado un número de técnicas bioquímicas para medir los niveles de tricíclicos en el plasma. Estos incluyen la cromatografía de gases con detectores, la cromatografía de gases con espectrometría de masas, los radioinmuno ensayos, el análisis con radio isotopos y la cromatografía líquida de alta presión. Este último método está probando ser de gran utilidad por su sensitividad y especificidad equivalente o superior a los métodos cromatográficos de gases.²⁵

Aún cuando se emplea un mismo método analítico, se puede encontrar una gran diferencia entre los niveles

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sanguíneos obtenidos en diferentes pacientes luego de usar la misma dosis oral.²⁶ Estos hallazgos indican que en los estudios con antidepresivos es más importante tomar en cuenta los niveles en plasma del antidepresivo que las dosis orales del mismo. Las diferencia pueden deberse también a factores hereditarios y metabolismo y absorción de la droga o a una interacción con otros medicamentos. Algunos neurolépticos pueden inhibir el metabolismo del antidepresivo aumentando su concentración en el plasma.²⁶

Usualmente la respuesta al tratamiento con antidepresivos se manifiesta luego de dos o tres semanas de recibir los mismos. Hay varias hipótesis que explican este fenómeno; 1) que el antidepresivo provoca un cambio en la síntesis de las aminas biogémicas pero toma tiempo en que estos neurotransmisores viajen al terminal sinóptico;²⁶ 2) tarda producirse cambios en los receptores presinápticos y postsinápticos en el sistema catecolaminérgico.²⁷

El presente estudio fue diseñado con el propósito de desarrollar un método preciso usando la cromatografía líquida de alta presión para determinar los niveles de amitriptylina en sangre. Además se intentó determinar si existe una correlación entre los niveles sanguíneos de amitriptylina y las puntuaciones de los factores de la escala Hamilton de depresión. (EHD)

Materiales y Métodos

El estudio fue realizado en siete pacientes (seis hombres y una mujer). Todos los pacientes llenaban los criterios diagnósticos de un trastorno de depresión mayor de acuerdo al DSM III. De estos siete pacientes dos habían sido diagnosticados como trastorno distímico y esquizofrénico respectivamente. La tabla I muestra un perfil por sexo, edad, diagnóstico y dosis de amitriptylina para cada paciente.

Inicialmente los pacientes fueron evaluados en la Sala de Emergencia del Hospital de Veteranos y admitidos a la Unidad de Tratamiento Intensivo de Psiquiatría (PICU). De ahí fueron trasladados a salas abiertas donde se llevaron a cabo los estudios. Los pacientes fueron cuidadosamente evaluados por lo menos por tres médicos. Se seleccionaron todos los pacientes disponibles en el momento del estudio que tuvieran un predominio de sintomatología depresiva y que consintieran a ser incluídos en el mismo.

Estos pacientes estaban recibiendo tratamiento con amitriptylina en dosis orales que fluctuaban entre 75 y 200 mg/día durante un período mínimo de seis semanas. Luego de las primeras dos semanas de tratamiento, los pacientes fueron evaluados con EHD por dos médicos.²⁸ Para una descripción de ésta y sus siete factores véase la tabla II.

Tabla II

Composición de EHD y Subdivisión en sus Siete Factores

FACTOR I - Ansiedad/Somatización

Ansiedad, psíquica Ansiedad, somática Síntomas somáticos, Gastrointestinales Síntomas somáticos, General Hipocondriasis Introspección

FACTOR II - Peso

Pérdida de Peso (historial) Pérdida de Peso (actual)

FACTOR III - Trastomos Cognositivos

Sentimiento de culpa Suicidio Agitación Depersonalización, Derealización Ideas paranoides Síntomas obsesivos y compulsivos

FACTOR IV - Variación Diurna

Variación diurna (tiempo) Variación diurna (Severidad)

FACTOR V - Retardación Sicomotora

Estado de animo deprimido Trabajo y actividades Retardación Síntomas genitales

FACTOR VI - Tratornos en el sueño

Insomnia temprana Insomnia intermedia Insomnia taría

FACTOR VII - Pesimismo

Desesperanza Desamparo Menosvalía

Tabla I
Perfil de los Siete Pacientes

	Term de los siete l'actines									
Número Asignado	Sexo	Edad	Peso (lb)	Diagnóstico	Tratamiento (mg p.o.)					
I	Н	49	206	Depresión mayor (D.M.)	Amitriptylina (AM) 25 mg tid, 50mg hs					
2	Н	51	120	D.M.	AM. 25 mg bid, 50 mg hs					
3	Н	32	155	D.M.	AM. 25mg AM, 50mg hs					
4	Н	55	180	Desorden distímico	AM. 25mg bid, 100mg hs					
5	Н	61	130	D.M.	AM. 50mg tid, 50mg hs					
6	M	39	125	Esquizofrenia con depresión	AM. 50mg qid Perphenazina 8mg qid					
7	Н	55	168	D.M.	AM. 50 mg bid, 100 mg hs					

Análisis Químico

En este estudio se utilizó la cromatografía líquida de alta presión (HPLC). El análisis de las muestras se puede resumir en tres etapas de acuerdo al método de la compañía Beckman.^{29, 30, 31} La primera etapa consiste en la preparación de reactivos. Las últimas dos etapas incluyen la extracción del antidepresivo y el cálculo de las concentraciones del mismo.

Primero se prepara una fase movil que será la que transportará la muestra a través del sistema cromatográfico. Esta se compone de la combinación de dos solventes (acetonitrito y metanol) con una substancia amortiguadora de fosfato de sodio a un pH de 7.0, (5m M Na₂ HPO₄ buffer).

Usando agua y metanol se eliminan todos los componentes del suero excepto la amitriptylina estudiada, la cual es retenida por las columnas de extracción tipo Bond-Elut. Utilizando otra mezcla de solventes (dietilamina y ácido acético) extraemos de las columnas el antidepresivo. El eluido obtenido se evapora en una atmósfera de nitrógeno a 70°C.

Una vez evaporado el solvente, la amitriptylina adherida a las paredes de los tubos colectores es diluída con 200 microlitros de la fase movil antes mencionada. De esta cantidad solo se invectan 20 microlitros por cada análisis al cromatógrafo, Modelo Beckman 334. Esta muestra es bombeada a través de una columna analítica empacada con C-N-Síclica. Estas columnas poseen la cualidad de permitir el paso de compuestos a diferentes velocidades según sus características físico-químicas. A medida que el compuesto va saliendo de la columna pasa a un detector de onda variable modelo Beckman 100-40 con una banda ultravioleta de 210 nm. La información aquí obtenida es integrada por una computadora Data Chromatopac, Altex, Modelo C-RIA con un impresor, el cual nos reproduce la información mediante un cromatograma y calcula la concentración de amitriptylina en ng/ml.

Análisis Estadístico

Los resultados fueron analizados en tres formas según se resume a continuación:

I. Comparación de valores entre la primera (pre-luego de dos semanas de farmacoterapia) y la segunda medida del estudio (post-luego de seis semanas de farmacoterapia).

Los resultados fueron analizados usando pruebas estadísticas no paramétricas para dos muestras repetidas, específicamente la prueba de rangos señalados y pares igualados de Wilcoxon.³² Se escogió esta prueba no paramétrica por varias razones tales como un número pequeño de pacientes y el que desconocemos si es o no un grupo representativo de la población general de pacientes veteranos de las Fuerzas Armadas deprimidos. Además, esta prueba es aplicable porque en nuestro estudio podemos ordenar significativamente las diferencias observadas para los diferentes pares igualados.³²

Mediante este análisis estadístico intentamos detectar algún posible cambio clínico en los siete pacientes durante dos diferentes períodos de tiempo de exposición al medicamento (pre = luego de dos semanas y post = luego de seis semanas). Todos los pacientes tenían síntomas de depresión mayor y cada uno fue su propio control. Utilizando la prueba no paramétrica de Wilcoxon confrontamos los valores obtenidos en la medición *pre* con los de la *post* buscando posibles diferencias significantivas entre éstas. Dichos valores comprenden los niveles séricos de amitriptylina en ng/ ml, las puntuaciones de la escala Hamilton de depresión y las de cada uno de sus siete factores. El nivel de significación usado en este método es de $p \le 0.05$.

II. Correlación entre los niveles séricos de amitriptylina, las puntuaciones totales de la escala Hamilton y la de sus siete factores.

Para esta etapa del análisis utilizamos el coeficiente de correlación de rango de Spearman³² el cual es útil en la medida de asociación de variables en escalas ordinales. Con este programa estadístico se confrontaron los niveles séricos de amitriptylina con las puntuaciones totales de la escala Hamilton de depresión y con los de cada uno de sus siete factores.

La tabulación ordinal de datos se ilustran en la tabla III (pre) y en la tabla IV (post). En estas dos tablas ordenamos en diez columnas verticales respectivamente: 1) el número asignado a cada paciente; 2) los niveles en sangre de amitriptylina en ng/ml; 3) las puntuaciones totales de Hamilton; y del 4 al 10 las de sus siete factores para las medidas pre (tabla III) y post (tabla IV). En siete columnas horizontales ordenamos los valores individuales de cada paciente paralas categorías antes mencionadas. Tomando como referencia los niveles séricos del antidepresivo, los ordenamos en forma descendente y por

Tabla III

	de sus ractores butante la rase rie									
Paciente	Niveles	Total	FI	F II	F III	FIV	F V	F VI	F VII	
1	722	26	6	0	5	2	5	5	3	
4	645	45	7	1	17	3	9	3	5	
3	468	37	9	3	5	3	8	5	4	
2	459	34	8	2	8	1	8	4	3	
5	254	17	4	1	3	2	1	6	0	
7	211	46	8	0	12	4	10	6	6	
6	142	29	9	1	8	2	4	4	1	

Valores Individuales de los Niveles Séricos de Amitriptylina, Valores Totales de EHD y Cada Uno de sus Factores Durante la Fase Pre

Tabla IV

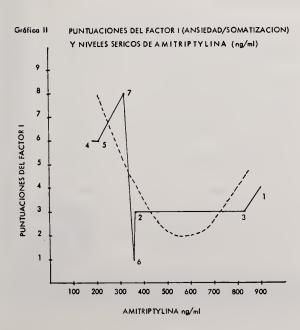
Valores Individuales de los Niveles Séricos de Amitriptylina, Valores Totales de EHD y Cada Uno de sus Factores Durante la Fase Post

Paciente	Niveles (ng/ml)	<u>Total</u>	FI	FII	<u>FIII</u>	FIV	F V	F VI	<u>F VII</u>
1	900	29	4	0	8	3	6	5	3
3	837	22	3	0	6	3	5	3	2
2	361	9	3	0	3	1	1	0	1
6	356	9	1	0	2	0	1	1	4
7	327	37	8	1	9	1	8	5	5
5	210	24	6	1	2	5	6	3	
4	187	31	6	1	10	2	5	4	3

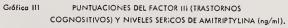
eso los números asignados a cada paciente en la primera columna vertical no están en orden.

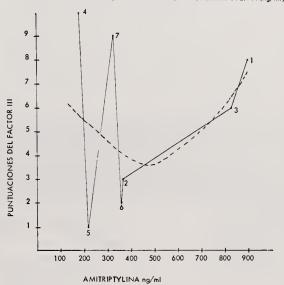
Extraimos los datos tabulados para construir gráficas (véase gráficas I, II, III y IV). En el eje vertical colocamos en orden descendente la puntuación de la escala Hamilton de depresión o la de alguno de sus factores (I,

Grófica I PUNTUACIONES TOTALES DE EHD Y NIVELES SERICOS DE AMITRIPTYLINA (ng/mi) 45 40 35 30 25 20 15 10 5 VENTANA TERAPEUTICA 200 400 500 700 800 900 AMITRIPTYLINA ng/ml

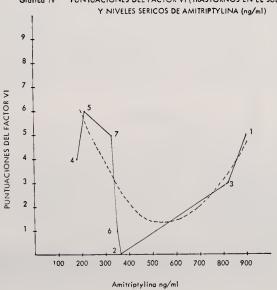


III y VI). En el eje horizontal situamos los niveles séricos de amitryptilina en orden descendente. Se hizo una gráfica de aquellos valores durante la fase Post que resultaron significantivamente diferentes ($p \le 0.05$) a sus controles en a etapa de la fase pre.





Gráfica IV PUNTUACIONES DEL FACTOR VI (TRASTORNOS EN EL SUEÑO)



Resultados

Los resultados de la fase pre y la fase post del estudio se resumen en las tablas III y IV respectivamente. (véase tablas III y IV). En el análisis estadístico, usándo la prueba no paramétrica de Wilcoxon, encontramos una diferencia significativa entre los valores obtenidos para la escala Hamilton en las fases pre y post del estudio con un nivel estadísticamente significativo p = 0.031. También se encontró una diferencia significativa entre los valores pre y post en las puntuaciones obtenidas para el factor I con un nivel de significación de p = 0.046. Es importante señalar que en los factores III y IV de la escala Hamilton encontramos también unas diferencias significativas entre los valores pre y post con p = 0.054 y P = 0.052 para cada factor respectivamente, sobrepasando por escasas milésimas el valor de p = 0.05establecido en este estudio como el límite superior de probabilidad de que los resultados fueron estadísticamente insignificantes.

Usando las correlaciones de rango de Spearman encontramos que hay una correlación significativa en a fase pre entre las puntuaciones totales de la escala Hamilton (EHD) y los factores III, IV, V y VII con unos niveles de probabilidad de p = 0.015, p = 0.031, p = 0.001 respectivamente. Para la fase post encontramos una correlación significativa entre las puntuaciones totales de EHD y los factores I, II, III, V y VI con unos niveles de probabilidad de p = 0.002, p = 0.032, p = 0.029, p = 0.004 y p = 0.037 respectivamente. Además se encontró una correlación negativa entre los niveles séricos de amitriptylina y las puntuaciones del factor II. No obstante, como habíamos visto usando la prueba de Wilcoxon en el análisis estadístico, este factor II no difiere significativamente entre sus puntuaciones de la fase pre y la fase post. Por lo tanto entendemos que la correlación encontrada entre el factor II y los niveles séricos de amitriptylina carece de validez.

Usando la prueba de Wilcoxon encontramos una diferencia significativa entre las fases pre y post para las puntuaciones totales de EHD, el factor I y marginalmente significativos para los factores III y VI de EHD. En las gráficas I, II, III y IV podemos observar una relación curvilínea entre los niveles en sangre de amitriptylina (ng/ml) y las puntuaciones de los valores de EHD y sus factores I, III y VI. En nuestro estudio, los niveles de amitriptylina que se asocian a unas puntuaciones menores de EHD y de sus factores I, III y VI tienen unos límites inferiores y superiores de 300 a 800 ng/ml.

Discusión

Este estudio demuestra un método sensitivo y útil para detectar los niveles de amitriptylina en la sangre. La sensitividad del método de 5 ng/ml sobrepasa los niveles detectados en nuestros pacientes que fluctuaron entre 142 a 900 ng/ml. Es un método útil para correlacionar los niveles de amitriptylina en la sangre con las pruebas clínicas que miden la severidad en la depresión.

Por razones del número reducido de pacientes nos vimos precisados a utilizar estadísticas no paramétricas. Como la prueba de Spearman no podía detectar una correlación curvilínea, sino positivos o negativos, fue necesario usar las gráficas con este fin. El estudio de las gráficas sugiere una posible correlación curvilínea entre los niveles de amitriptylina en sangre y las puntuaciones de EHD y sus factores II, III y VI respectivamente. Los niveles séricos de la posible ventana terapéutica encontrada en nuestro estudio tiene unos límites inferiores y superiores de 300 a 800 ng/ml respectivamente para los cuales encontramos las menores puntuaciones en EHD y sus factores I (ansiedad y somatización), III (trastornos cognoscitivos) y VI (trastornos del sueño). Es posible que los valores que hemos obtenido resulten ser más altos que los que obtuvo Montgomery.²² (77-197 ng/ml) debido a la mayor sensitividad de nuestro método.

También determinamos que tanto en la fase pre como en la post las puntuaciones de los factores II (disturbios cognoscitivos) y V (retardación psicomotora) fueron los que mejor correlacionaron con las puntuaciones totales de EHD. Esto indica que estos factores fueron los que más determinaron la puntuación total de EHD en nuestro estudio.

Consideramos que la estimación de los niveles séricos de antidepresivos tricíclicos puede ser de utilidad para detectar pacientes que no cumplen con el tratamiento o que no metabolizan adecuadamente los mismos lo que puede conllevar el que se obtengan niveles muy bajos o tóxicamente altos en los mismos. El desglosar la EHD en sus siete factores puede ayudar a determinar los subcomponentes clínicos que cambian más con el tratamiento y cuáles se relacionan mejor con los niveles séricos del antidepresivo. Los hallazgos obtenidos en este estudio piloto, aunque no pueden considerarse como definitivos, señalan una posible relación curvilínea entre los niveles séricos y los síntomas clínicos, lo cual amerita futuras investigaciones con un mayor número de pacientes.

Reconocimiento

Los autores reconocen la ayuda de la Dra. Ilsa Echegaray y el Sr. Abraham Rosa del Departamento de Psicología de la Universidad de Puerto Rico.

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ARTICULOS ESPECIALES

Risk Factors of Atherosclerosis in Children and Adolescents

Detlef Kunze, M.D.*

yocardial infarction is preceded by a series of events leading to atherosclerosis with several risk factors interacting. Many individuals remains asymptomatic until they develop serious complications and the disease is progressing unnoticed over many years. If prevention is to be successful, we must try to identify individuals at risk as early as possible, even in childhood.

According to well established evidence, atherosclerosis may originate in childhood. However, there are many open questions as to its pathogenesis and to ways of diagnosis and treatment at this early stage.^{5, 9, 10}

Atherosclerosis is a multifactorial process subject to both genetic and environmental factors.⁷ The following five risk factors must be emphasized:

- hyperlipidaemia
- high blood presure
- smoking
- obesity
- family history.

These predisposing conditions will be commented upon and their early identification in the population will be referred to as the prerequisite for preventive measures.

Hyperlipidaemia

There are apparently three types of genetic hyperlipidaemias which lead to vascular lesions identical to those of degenerative atherosclerosis. Incidence and mode of inheritance are specific for each of these genetic diseases of lipid metabolism. They are listed below according to their respective frequency:

- 1. Familial combined hyperlipidaemia (3-15/1,000, autosomal dominant)
- 2. Familial hypercholesterolaemia (1-2/1,000, autosomal dominant)
- 3. Familial type III hyperlipoproteinaemia (0.2/1,000, multifactorial).

A high fat intake and other dietary habits have been identified as the most important environmental factors. A WHO Expert Committee ¹² has established normal limits of cholesterol which, however, vary considerably with age and in different countries. It is a well known fact that the average blood cholesterol level is much higher in western countries than in Japan, for example, and that in the former the incidence of coronary heart disease is also higher. ¹² As far as hyperlipidaemia in childhood is concerned, we have to realise that the levels of nearly all lipid fractions rise rapidly in infancy (at birth they are one third, in early infancy half the adult level), remain more or less constant in later childhood and drop at puberty. ⁴, ⁸, ¹¹ In general, too little attention has been paid to blood lipid levels in children.

Categories of lipid studies in children should be classified as follows:^{5, 11}

- LDL-cholesterol level in cord blood in cases of familial hypercholesterolemia in at least one parent
- total cholesterol after the age of 4 if there is a family history of coronary heart disease, peripheral occlusion or cerebro-vascular disease before the age of 55
- total cholesterol irrespective of age in the presence of clinical symptoms or at venipunctures for other reasons.

Hypertension

As blood pressure in children rises with age, the measurement in an individual child should be referred to as percentile graph (similar to the graphs available for weight and height). All studies indicate that approximately 5% of children are hypertensive and that their blood pressure remains abnormally high into adolescence and adulthood. It is therefore important to start early in life preventive measures, particularly with regard to sodium intake, which should be reduced to less that 5 grams a day, and control of overweight.

Smoking

Smoking is of increasing importance as a risk factor of atherosclerosis. There is a critical period between 11 and 13 years of age, when occasional smoking may develop into habitual smoking. Thirty percent of the youngsters between 13-18 years, in the western industrialized

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countries, are smokers, girls showing a higher incidence than boys. Therefore, prevention of degenerative vascular disease must start before the age of 13. Later in life, the general behaviour, smoking and eating habits, will be too strongly fixed for educational influences to succeed.^{5, 9, 13}

Obesity

Like atherosclerosis, obesity is a multifactorial phenomenon. The result is an excessive deposition of fat with an increase in the number and volume of fat cells. The subcutaneous fat tissue can be measured with a skinfold caliper in a standardized way. Analogous to the rise of normal lipid values, we notice a marked increase of subcutaneous fat in infants—with figures doubling between birth and about 9 moths of age—followed by a slight drop and another rise at puberty.⁴

How to control the "epidemic"?

On the basis of a WHO study in five European cities, 10 a high frequency of atherosclerosis in children between 10 and 14 years of age has been established (10% of 18,000 autopsies!). Beyond this epidemiological data information about the individual's risk is needed, partially obtainable by a serum cholesterol screening. This could be carried out within the framework of a health education programme such as the KYB-programme of the American Health Foundation, which is now also being introduced in some other countries.9, 13 On the other hand, the genetic risk has to be taken into account. These two criteria, together with behavioural and other environmental data, may be combined in a prognostic score based on epidemiological investigations.7 Many high risk individuals may be identified on the basis of a family history; siblings of patients with premature coronary heart disease showed an increased prevalence of hypertension (37%) and hyperlipidaemia (19%). Not only between siblings but also between parents and their children a strong correlation of LDL-cholesterol levels has been established.² Moreover, even in children and their grandparents a correlation has been found between coronary heart disease in the latter and the grandchildren's HDL/LDL-cholesterol ratio.6

In spite of a fairly wide recognition of these facts among the medical profession, there is still too little active engagement to change dietary habits.³ This is regrettable, as a large part of the society is taking a positive attitude towards these preventive ideas.³

Practical recommendations

Even in childhood excesses should be controlled and reduced: lipid levels, blood pressure, smoking and body weight.

High blood lipid levels in children are in many countries the result of national dietary habits. The recommendations for reducing blood cholesterol in adults are analogous for children. Therefore physicians and the general public must be made more familiar with strategies aimed at lowering high blood cholesterol levels by dietary intervention:

 Breast milk, though rich in cholesterol, is still regarded as optimal, probably because it stimulates lipoproteinlipase activity. But the mother's diet is important as it determines the quality of breast milk: in populations with a low intake of saturated fats, the breast-fed infants ingest more polyunsaturated fatty acids, and their serum cholesterol levels are lower. Similarly, infants fed adapted formulas that contain less cholesterol and more polyunsaturated fat do not show the high increase of serum cholesterol during the first weeks of life.

- Total fat intake in children and adolescents should not exceed 25% and saturated fat intake should not be more than 10% of calories. The recommended P/S ratio (polyunsaturated fatty acids to saturated fatty acids) is 0.75-1.0.
- Cholesterol intake should be reduced to 100 mg per 1,000 calories and should not exceed 300 mg per day.
- Lean meat, fish and poultry are recomended.
- Consumption of fruits, vegetables and whole grains should be encouraged.
- School children, especially in cases of overweight, should consume milk products with reduced fat content. Overweight in childhood is usually caused by a high intake of sugars (sweets and lemonades) and fat, leading to an increased endogenous production of triglycerides and cholesterol. Therefore restriction of calorie intake and increase of energy expenditure are necessary.

All primary preventive efforts should start in childhood to inhibit the development of early atherosclerosis. The medical profession should cooperate with educators, communities, industry and private initiatives in a combined programme, emphasizing a healthy life style.

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DIAGNOSTICO ANGIOCARDIOGRAFICO



Rafael Villavicencio, M.D., F.A.C.C.* Angel F. Espinosa-López, M.D.* Lynnette Budet, M.D.**

Un niño de 10 meses de edad se hospitaliza para un cateterismo cardíaco. Tiene historial de soplo desde el período neonatal, fallo cardíaco a los dos meses de edad y cianosis discreta al llorar, esta última de aparición reciente. Ha tenido varias hospitalizaciones en los últimos meses por bronconeumonías e insuficiencia cardíaca a pesar de tomar digoxin. Su aumento de peso ha sido muy lento, no fue hasta hace 2 meses que logró duplicar su peso al nacer.

En su examen de admisión se apreciaba un infante distrófico, acianótico y taquipneico (80/min). La frecuencia cardíaca era de 140/min y su presión arterial normal. Tenía un precordio activo, con accesibilidad ventricular derecha y frémito ("thrill") en los espacios intercostales 3 y 4 del margen esternal izquierdo. Había un soplo pansistólico, rudo, grado 4/6 a lo largo del reborde esternal izquierdo, el S₁ estaba normal y el S₂ se desdoblaba bien pero con un componente pulmonar acentuado. Se apreciaba también un arrastre diastólico leve en punta. Tenía hepatomegalia discreta (3cm bajo el reborde costal derecho) y los pulsos femorales estaban normales.

La Hb era de 14gm., el electrocardiograma revelaba hipertrofia ventricular derecha, desviación del eje QRS a la derecha (+120°) e intervalo PR discretamente prolongado (0.16 sec). La radiografía de tórax reveló cardiomegalia con un segmento pulmonar prominente e hipervolemia pulmonar arterial.

La figuras 1 y 2 son representativas del angiocardiograma que se le hizo.

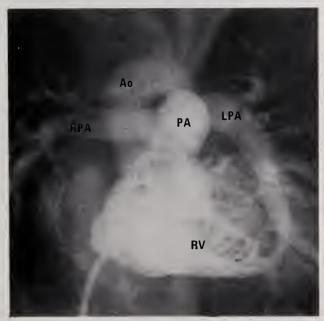


Figura 1. Angiocardiograma del ventrículo derecho en posición AP. PA: arteria pulmonar, LPA: arteria pulmonar izquierda, RPA: arteria pulmonar derecha, RV: ventrículo derecho, AO: aorta

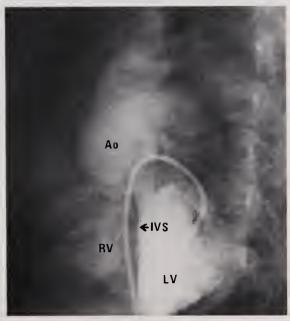


Figura 2. Ventriculograma izquierdo en posición LAO, LV: ventrículo izquierdo, IVS: septo interventricular, AO: aorta, RV: ventrículo derecho

¿CUAL ES SU DIAGNOSTICO?

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Ventrículo Derecho de Doble Salida

El ventrículo derecho de doble salida (VDDS) es una cardiopatía congénita rara que se produce por anomalías en el desarrollo troncoconal. Su incidencia es de aproximadamente 0.10 por 1000.1 Debido a las alteraciones troncoconales las dos grandes arterias salen del ventrículo morfológicamente derecho (figura 1) existiendo con frecuencia discontinuidad mitroaórtica y la única salida del ventrículo izquierdo la constituye una comunicación interventricular.

La definición prevalente para VDDS es aquella condición en la cual ambos troncos arteriales emergen completamente del ventrículo derecho con musculos infundibulares bilaterales y ausencia de continuidad atrioventricular-semilunar.2 En cambio Kirklin y colaboradores son más laxos en este sentido y definen el VDDS como "aquella malformación en la cual la totalidad de una arteria y más de la mitad de la aorta se originan del ventrículo derecho."3 Aparte de estas consideraciones es muy importante en los casos de VDDS el reconocer la relación entre los grandes vasos, la localización de la comunicación interventricular (CIV) y la presencia de estenosis pulmonar.

Hay cuatro variantes en la relación de los grandes vasos, estas son:

- relación normal— el tronco pulmonar está anterior y a la izquierda de la aorta.
- relación lado a lado— la aorta está a la derecha de la arteria pulmonar y las válvulas semilunares están aproximadamente en el mismo plano horizontal.
- dextroposición— la aorta está a la derecha y anterior a la arteria pulmonar.
- levoposición— la aorta está a la izquierda yanterior a la arteria pulmonar.

La relación lado a lado es la "clásica" de las grandes arterias en los casos de VDDS.

Salvo muy raras excepciones los casos de VDDS tienen una CIV. La posición de esta CIV puede ser:

- sub aórtica— la CIV está más cerca de la válvula aórtica que de la pulmonar. Es la localización más frecuente en VDDS (57%).
- sub pulmonar— CIV más cerca de la válvula pulmonar (32%). Cuando la CIV está localizada sobre la cresta supraventricular a este tipo de VDDS se le denomina anomalía de Taussig-Bing.
- doblemente comprometida— CIV muy grande, guarda relación cercana con ambas válvulas semilunares. Suele estar sobre la cresta supraventricular y extenderse de forma oblicua bajo los dos grandes vasos.4
- remota o no-comprometida— la CIV está distante a ambas válvulas semilunares. Puede ser una CIV posterior, muscular aislada o del tipo A-V canal, siendo esta última la más frecuente de las "remotas".5

Como podemos ver, basándonos en cuatro formas de relación entre los grandes vasos y cuatro posiciones de la CIV hay 16 posibles combinaciones de VDDS solamente considerando estas dos variables.

En la clasificación fisiológica de Neufeld^{6, 7} el VDDS se

dividió en dos grandes grupos dependiendo de la presencia o ausencia de estenosis pulmonar. En presencia de estenosis pulmonar los hallazgos clínicos, electocardiográficos, radiográficos y hemodinámicos son muy parecidos a los de la tetralogía de Fallot. Muchas veces es solo mediante la angiocardiografía que pueden diferenciarse estas dos entidades. En los pacientes con VDDS sin estenosis pulmonar (como lo es el caso que ilustramos) los hallazgos son muy parecidos a los de aquellos niños con CIV y corto circuito de izquierda a derecha grande o a los que ya tienen corto circuito dominante de derecha a izquierda con enfermedad vascular pulmonar obstructiva.

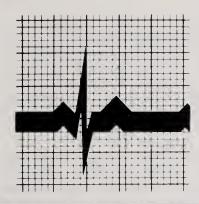
Las características angiográficos del VDDS dependerán por consiguiente de la presencia de estenosis pulmonar, la localización de la CIV y la relación entre los grandes vasos. Sin embargo, podemos decir que en términos generales los criterios angiográficos para el diagnóstico de VDDS son: la opacificación de ambos grandes vasos de el ventrículo derecho, visualización de las válvulas semilunares en el mismo plano horizontal, malposición de la aorta y la presencia de un defecto de llenado de aspecto lingular en la base del ventrículo derecho formando una "división" entre ambos tractos de salida. Estas características angiocardiográficas pode-

mos observarlas en las figuras 1 y 2.

El tratamiento quirúrgico del VDDS se complica con la gran variabilidad morfológica intra y extracardíaca que pueden presentar estos pacientes. Debido a la complejidad anatómica de estos corazones es preferible hacer cirugía paliativa en aquellos infantes que desarrollan síntomas. La constricción quirúrgica ("banding") de la arteria pulmonar en los pacientes sin estenosis pulmonar protegerá las arteriolas pulmonares de la arteriopatía pulmonar obstructiva. Las anastomosis sistémicopulmonares en los infantes con estenosis pulmonar aumentan el flujo pulmonar, reducen la cianosis y se evitan los accidentes hipóxicos con sus graves consecuencias. La reparación completa del VDDS dependerá de la complejidad anatómica de cada caso. Idealmente este tipo de cirugía suele posponerse hasta los 2-4 años de edad, dependiendo del procedimiento quirúrgico que se contemple.

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ELECTROCARDIOGRAM OF THE MONTH

Charles D. Johnson, M.D., F.A.C.C.

This 81-year-old female presented with the symptoms and signs of congestive heart failure. The pulse was 45 bpm and the blood pressure 180/108 mm Hg.

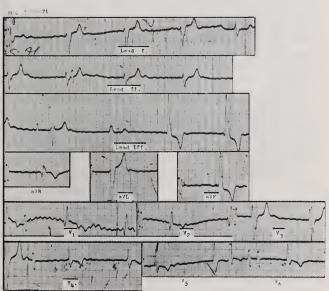


Figure 1

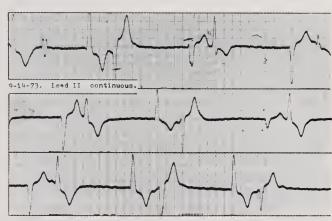


Figure 2

Questions

- 1. What are the electrocardiographic diagnoses?
- 2. Is a cardiac pacemaker indicated? Which type?

Answers

Figure 1. Atrial fibrillation (Af) or flutter-fibrillation, with a slow ventricular escape response (VEBs) of 31.9 -37.5 bpm, representing a Sick Sinus Syndrome and high grade (HG), near complete atrioventricular (AV) block. The Q-T interval = 0.56 S. There is suggestive bilateral third degree bundle branch block (BBB) or trifascicular block (TB) with the escape foci being idioventricular, from the left ventricle (LV), rather then AV junctional block with an escape junctional/His bundle focus and complicating bifascicular blocks (alternating right BBB + left anterior hemiblock, LAH- first and fifth in lead I and first in lead III- and right BBB + left posterior hemiblock, LPH- last two beats in lead III), a TB also. There may be two or three ventricular escape foci, yet the third beat in lead III suggests a ventricular fusion beat (VFB) between two escape ventricular foci. The last two beats in this lead have the appearance of LPH beats and could represent fascicular escape beats with their origin near the left anterior fascicle of the LV.

Figure 2. Apparently, a continuous lead II. Af, very slow VEBs with rates of 30-38 (1580-2000 ms). VEBs manifest multiform morphologies and are bidirectional (positive and negative), suggesting multifocal VEBs. The penultimate beat in the middle strip could be a VFB. Ventricular ectopy or premature beat (VPB), as bigeminy, follows each VEB, with coupling intervals ranging from 560-680 ms, but not correlating consistently with the preceding escape interval. The VPBs also manifest multiform morphologies, and bidirections. The last VPB in the upper row could be a VFB. The VEBs and the VPB may arise in similar ectopic ventricular sites. The VPBs are not likely to reflect ventricular reciprocal (echo) beats of ventricular origin (subatrial reentry), nor ventricular parasystole in spite of the slightly variable coupling, only slightly different VPB-VPB interval and suggestive VFBs.

If the AV block were junctional rather than infranodal bilateral third degree BBB (TB), persistent right BBB and alternating LAH and LPH in both the VEBs and in the VPBs, could be appropriately hypothesized. If so, phase 4 right BBB with either LAH or LPH in the junctional escape beats, and either phase 3 LAH or LPH in the junctional premature beats, could exist.

The VPBs are similar in context to Type III bidirectional ventricular tachycardia. The "Rule of Bigeminy", the tendency of VPBs to be precipitated by longer R - R intervals, can be invoked to explain the ventricular bigeminy in Figure 2. A permanent epicardial, demand VVI pacemaker was implanted.

Discussion

Complete AV junctional block with bifascicular intraventricular conduction block must be differentiated from bilateral third degree BBB. Complete AV junctional block manifests first clinically, a faster (35-50 bpm) more stable, normal width idiojunctional escape rhythm, Wenckebach periods more commonly, is preceded by a quite prolonged P-R interval; if fluctuation occurs, one or two basic QRS complexes with sharp transition between without rate change, and if any aberration of conduction

exists this is typical right or left BBB; it occurs in inferior myocardial infarction. The latter manifests a multiform bizarre atypical pattern not resembling either classic right or left BBB, at a rate 35, with fluctuating QRS patterns with rate changes, preceded by a slightly prolonged or normal P-R interval, alternating or intermittent BBB pattern or right BBB and LAH; electrocardiographic manifestations precede clinical effects; it is characteristic of anterior infarction (Schamroth).

In complete AV block the ventricular rhythm may be irregular because of an unstable ventricular pacemaker, an irregular exit block, or two or more multifocal, multiform idioventricular pacemakers because each focus usually possesses a different discharge rate or cycle. One pacemaker focus can change to another, since both are located in the same biventricular chamber. The faster escape impulse, or a VPB, raches, discharges prematurely, abolishes and resets the other escape focus. In Af, due to concealed conduction, there is a pause following the extrasystole, which is incomplete. This can initiate a period of ventricular standstill or accentuate the irregularity; nodal escape may fail to occur and two or more long cycles may occur in succession.

Extrasystoles may complicate HG and complete AV block. They may manifest as unifocal, unifocal with abnormal intraventricular conduction, multifocal, as pairs or as a bigeminal pattern. Bifocal VPBs tend to present in bigeminy alternating from one focus to another.

A VFB can infrequently result from the combination of an AV junctional and an ectopic ventricular beat. Rarely, but especially in complete AV block, two idioventricular pacemakers or VPBs from two or more foci can produce a VFB; the diagnosis is stated to be difficult to impossible, but the timing and configuration may be of aid.

The VPBs were probably of multifocal origin with alteration, but a unifocal origin with aberration of conduction, junctional with BBB aberration plus extrasystolic ventricular bigeminy, and a ventricular circus movement are other considerations.

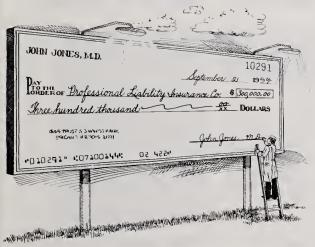
Severe digitalis intoxication can induce a sagging ST segment, multiform ventricular bigeminy and HG, perhaps complete AV block, from combined excitant and suppressive actions.

Advanced pacemaker and conducting tissue disease was present, and a cardiac pacemaker was obviously indicated. A VVI unit was appropriate because in chronic Af an atrial tracking pacemaker is not applicable. Type 1 and beta blocker antiarrhythmic agents are contraindicated for VPBs complicating complete heart block.

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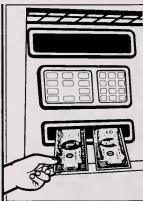
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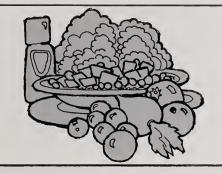






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MEDICAL ASPECTS OF NUTRITION

The Use of Whole Cow's Milk in Infancy*

Previous statements of the Committee on Nutrition have focused on infant feeding during the first 6 months of the life. The purposes of this statement are to update recommendations concerning infant feeding during the second 6 months of life and to suggest futher needed research in this area.

Whole Cow's Milk and Iron

The appropriate age at which unheated, whole cow's milk (WCM) can be safely introduced into the infant diet is unknown and remains an area of controversy. In numerous reports, the consumption of excessive amounts of WCM has been associated with iron-deficiency anemia.1-4 This is partly due to the fact that both the concentration and the bioavailability of iron are low in milk. Also, WCM can cause occult bleeding from the gastrointestinal tract. The process by which this occurs is unknown, but Eastham and Walker, in a review of the effects of cow's milk on the gastrointestinal tract, classifield the mechanisms involved as enzymatic, toxic and immunologic.5 They suggested that the occult blood loss and exudative enteropathy syndrome following cow's milk ingestion are more likely toxic in nature because no classic immunologic mechanism has been demonstrated. However, the exact mechanims(s) for these conditions have not been established.

Although studies have shown an association between WCM consumption and anemia, there are some difficulties in using these findings as a basis for recommendations for feeding older infants. ¹⁻⁴ This is because of the young age at which the infants studied were initially given WCM. In one of the studies, ¹ WCM was introduced at age 2 months; in another study, ⁴ WCM was introduced at less than 4 months of age, although the precise age was not mentioned; and in a third study, ³ the age was not specified. If the developing gut is more vulnerable early in

life, it is possible that the deleterious effects of WCM may be avoided by delaying the age at which it is first introduced.

The consequences of feeding WCM for the first time to older infants have been examined in only one study,6 which will be considered here in some detail. Fomon, et al., studied 81 normal infants, aged 112 to 196 days, who had not previously consumed WCM: 39 infants were fed WCM and 42 were fed either a commercial infant formula or heat-treated cow's milk. All infants received a daily supplement containing 50 mg of ascorbic acid and 12 mg of iron as ferrous sulfate. The proportion of infants between 112 and 140 days old who had guaiac-positive stools (as determined by the Hemoccult slide [Smith, Kline Diagnostics, Sunnyvale, CA]) was significantly greater among infants fed WCM than among those fed Enfamil or heat-treated cow's milk. The infants fed WCM also had a significantly greater number of guajacpositive stools than the other infants. However, after 140 days of age, there was no difference between groups in the number of guaiac-positive stools. Furthermore, in these infants given iron supplements, no significant differences were observed between feeding groups in mean hemoglobin, hematocrit, serum iron, total iron binding capacity or trasferrin saturation measurements. Hematologic values did not differ significantly between infants with and those without guaiac-positive stools. Fomon, et al., concluded that WCM should not be fed before 140 days of age.6 Although the study demonstrated no adverse effects from feeding WCM after 140 days of age it must be noted that all infants were receiving a daily supplement of ferrous sulfate. Occult blood loss and iron status have not yet been studied in a group of older infants not receiving supplemental iron. Until such a study is conducted, the role of WCM in producing irondeficiency anemia in older infants remains unknown.

Cow's Milk Allergy

Another area requiring futher research is cow's milk-protein intolerance or "allergy." The incidence of milk-protein intolerance has been estimated at from 0.4% to 7.5% of the infant population in the strictness of the diagnostic criteria.

Committee on Nutrition, American Academy of Pediatrics, 141 NW High Point Road, P.O. Box 927, Elk Grove Village, Illinois 60007

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As is true of the reports about anemia, 1-4 many cases of unheated cow's milk-protein allergy are reported, but few are applicable to the question, at what age is it safe to first give an infant WCM? In some studies 1, 8, 9 in which infants showed allergic reactions, cow's milk frequently was introduced when the infant was less than 4 months old; in one study 10 in which infants were given formulas with a cow's milk base, there were allergic reactions within the first week of life. Moreover, differentiation has not always been made between WCM and processed formula.

Even if there is agreement that 0.4% to 7.5% of infants have cow's milk-protein allergy, this is a relatively small proportion of the population. Whether the percentage would decrease if cow's milk protein were withheld from the infant died for the first 4 to 6 months of life is not known. Before a definite recommendation can be made, well-designed studies are needed to evaluate the allergic response in older infants who have had no prior exposure to cow's milk protein.

Renal Solute Load of Whole Cow's Milk

A third factor about which there is little direct evidence is whether the renal solute load of WCM would be too high for an older infant. A recent study (G.H. Johnson: The effect of substitution of whole cow's milk for infant formula and breast milk in the diet of infants, unpublished data available from Gerber Products Co.), using diet diaries, attempted to examine the theoretical effect of substituting WCM for either breast milk or formula in infants 2 to 12 months old. The solute load imposed by the original diets and the cow's milk-substituted diets of the infants surveyed were compared using estimates based on the method of Ziegler and Fomon.¹¹ Results showed that substituting WCM for infant formula or breast milk would have resulted in an increase in urine osmolarity at all ages. However, this increase was more dramatic during the first 6 months of life (49.2% increase) than during ages 7 to 12 months (18.2%). The urine concentrations calculated from cow's milk-substituted diets were well within the range tolerated by infants, if the infants had access to water during hot wather or episodes of diarrhea.¹²

Defatted Milks

The feeding of reduced fat-content milk is not recommended during infancy. Fomon, et al., have observed that, although infants fed skim milk ad libitum continue to gain weight, they do so at a slower rate than infants fed formula or whole milk. Infants fed skim milk also show a rapid decrease in skinfold thickness, suggesting that body energy stores are being depleted. Although the consequences of rapidly decreasing body stores of fat during infancy are unknown, the effects may be unfavorable.

Use of Solid Foods

Solid and semisolid baby foods, or beikost, may be introduced when the infant is between 4 and 6 months, old, depending on neuromuscular maturation and whether the infant is satisfied with breast milk or formula as the sole source of nutrients. Solid foods should be

added individually, allowing several days to a week between the introduction of each new food, so food intolerance can be identified. Infant cereals fortified with electrolytic iron are a good choice as one of the first supplement foods. Three level tablespoons of dry infant cereal diluted with WCM of formula provide approximately 7 mg of iron. Commercially prepared combinations of cereal and fruit, which may be given to older infants after tolerance for individual components has been established, provide approximately 5 mg of iron per $4^{11}/_{2}$ -ounce jar. 1^{14}

Concerning the appropriate age of introduction of WCM into the infant diet, Formon, et al., ¹³ suggested that when an infant more than 6 months old is eating approximately 200 gm of beikost daily (the equivalent of approximately 1¹/₂ jars of strained food commercially prepared for infants), there is no objectionto feeding homogenized, vitamin D-fortified whole milk. As discussed here, both occult blood loss from the gastrointestinal tract and allergic reactions can occur, but most reports of these effects of introducing WCM have been in infants less than 6 months old, ^{1,6} or those fed in excessive amounts. ¹⁻⁴

Iron Status

The iron status of the 6-to 12-month-old infant depends mainly on whether most of the infant's calories come from human milk, an iron-fortified commercially prepared formula, or whole cow's milk, and/or an iron supplement is consumed on a regular basis.

When either human milk or WCM accounts for a major portion of the total calories ingested by older infants, an additional iron source is necessary. The most convenient source of iron for an infant on formula is an iron-fortified formula. For an older infant receiving human milk, cow's milk or a formula that is not iron-fortified, the best source of supplemental iron is iron-fortified cereal. The source of supplemental iron is iron-fortified cereal.

Research Needs

There are many unanswered questions concerning the use of WCM in the second half year of life including:

- 1. What is the rate and variability of maturation of infant gastrointestinal function?
- 2. What is the relative importance of the amount and bioavailability of iron in the total diet when WCM is substituted for iron-enriched formula at 6 months of age? Does iron-fortified cereal meet the infant's need for iron?
- 3. Can the change to cow's milk when the infant is 6 months old produce anemia from occult blood loss when the milk is fed in excessive amounts and there is no iron supplementation?
- 4. What is the relative importance of the high-solute load of WCM in the total feeding regimen of a 6- to 12-month-old infant? For example, how much of the high-solute load of WCM is diluted out by other foods in the diet?
- 5. What is the relative importance of the nutrients not present in WCM but present in infant formula and breast milk, i.e., essential fatty acids, tocopherol, ascorbic acid? How much of these nutrients are obtained from the other foods commonly used in the 6- to 12-month age group?

Conclusions

Breast feeding with appropriate supplementation is the preferred method of feeding infants 6 to 12 months old. Although many mothers will continue to breast feed or formula feed their babies through the first year of life, there is at present no convincing evidence from well-designed research studies that feeding whole cow's milk after 6 months of age is harmful if adequate supplementary feedings are given.

Research to answer the crucial questions discussed here must be carried out before firm recommendations can be made concerning the age at which it is safe to introduce WCM in infants' diets. Until these questions can be answered, the following recommendations for feeding infants 6 to 12 months old pertain.

If breast feeding has been completely discontinued and infants are consuming one third of their calories as supplemental foods consisting of a balanced mixture of cereal, vegetables, fruits and other foods (thereby assuring adequate sources of both iron and vitamin C), whole cow's milk may be introduced. The amount fed should be limited to less than 1 L daily. Most infants who are not breast fed should be consuming a significant portion of their calories from supplemental foods after they are 6 months old; those who are not should be given an iron-fortified formula.

Reduced fat-content milk is not recommended during infancy.

This is reprinted with the permission of the American Academy of Pediatrics. Since the publication of this statement in Pediatrics in August, 1983, some individuals have expressed reservations about the recommendations, based primarily on a concern for iron nutriture of the infant fed whole cow's milk during the seconc six months. The committee statement covers this area and no new studies appeared that indicate a need for any modification.

Alvin Mauer, M.D.
Chairman
Committee on Nutrition
American Academy of Pediatrics

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- Máximo período de beneficios Pagaderos hasta los 65 años de edad. Si la incapacidad comienza luego de los 65, el período máximo de beneficios es de 2 años. (La opción de pago de beneficios por vida está disponible).

- Incapacidad total presuntiva Se considera incapacidad total la pérdida total de la vista, habla, oído o de dos miembros, aún si continúa trabajando en su ocupación. Además, se le releva del período de espera y se le pagan beneficios por vida, aún si su período de beneficios cubre sólo hasta los 65 años de edad.
- Beneficio por rehabilitación Le permite participar en un programa aprobado de rehabilitación ocupacional y todavía recibir beneficios por 6 meses, aún si cesa de estar incapacitado.
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CHEST PAIN OF ESOPHAGEAL ORIGIN

This is a comment on the leading article of the July issue of the "Boletín" entitled "Chest Pain of Esophageal Origin". Dr. Wilmer Rodríguez is the author.

I centainly agree with his message. We should not overlook the esophagus as a cause of chest pain. Yet, there are two considerations that merit their addition to the practical and timely article.

First, I believe that foreign bodies lodged in the esophagus should also be included in Table I as another

cause of chest pain of esophageal origin.

Second, not always must heart disease be excluded before one may suspect an esophageal etiology. About 20 years ago, I was involved in such a case. I refer to a 65 year old male with a history of two previous myocardial infarctions who was brought to the emergency room complaining of chest pain. A diagnosis of an acute myocardial infarction was made and the patient was assigned to my service. After going through very worried moments, a soup bone was found lodged above the esophago-gastric junction and was removed with complete relief of symptoms. By the way, the barium swallow was negative. This case was published in the Boletín AMPR 56:69, 1964 under the title of "Foreign Body in the Esophagaus Simulating Myocardial Infarction".

José M. Torres-Gómez, M.D., F.A.C.P.

REFLEXIONES DE UN ANESTESIOLOGO

Para algunos colegas médicos la anestesiología es sencillamente sinónimo con la práctica de la administración de anestesia. Para otros es sinónimo con la supervisión de técnicos que administran la anestesia y para otros, afortunadamente pocos, las funciones del anestesiólogo son únicamente intervenir para "corregir" los problemas ocasionados por reacciones adversas a la anestesia o errores cometidos en su administración por personal técnico.

Mientras existan esos colegas, mientras no éste claro en la mente de todos los médicos cuáles son las verdaderas funciones del anestesiólogo, existirá confusión sobre si la anestesiología es una especialidad médica y/o si la práctica de anestesiología es la práctica de la medicina.

Es necesario que se haga tradicional la aceptación de cuales son las funciones y los deberes del anestesiólogo con sus pacientes. Mientras el comportamiento de los mismos anestesiólogos no demuestre totalmente esa aceptación de sus responsabilidades, existirá la duda entre otros muchos de la misma profesión médica, los profesionales aliados a la salud y los legos, políticos, legisladores y la comunidad en general.

He aquí la definición de anestesiología según el Departamento del Trabajo de los Estados Unidos y la Sociedad de Anestesiólogos Americana:

Anestesiología es la práctica de medicina que trata, pero no se limita a:

- 1) El manejo de procedimientos para rendir al paciente insensible al dolor y estrés emocional durante procedimientos quirúrgicos, obstétricos y ciertos procedimientos médicos.
- 2) Mantener las funciones vitales durante el estrés de manipulaciones anestésicas y/o quirúrgicas.
- 3) Manejo del paciente inconsciente por cualquier causa.
 - 4) El manejo para el control y alivio del dolor.
- 5) El manejo de problemas de resucitación cardíaca y/o respiratoria.
- 6) La aplicación de métodos específicos de terapia por inhalación.
- 7) El manejo clínico de problemas de equilibrio electrolítico, de líquidos o disturbios metabólicos.

Pretender reconocer estas funciones del anestesiólogo solamente cuando se le necesita en una emergencia o por razones personales no propicia ni conduce al mejor cuidado médico total de todos nuestros pacientes. ¡Y es precisamente esta la meta por la cual todos los médicos debemos luchar!

Miguel Colón Morales, M.D. Director Depto. Anestesiología Hospital del Maestro Hato Rey, Puerto Rico

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El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo; materiales y métodos) deben identificarse con un encabezamiento en letras

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Ártículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: Introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias.

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Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea. Se usará con preferencia el sistema métrico de pesos y medidas.

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In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

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The entire manuscript, including legends and references should be typewritten double spaced in TRIPLICATE with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgement of financial sponsors, and if the paper has been presented at a meeting the place and date should be given.

The manuscripts should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by headings in capital letters.

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FREQUENCY OF HEART ATTACK AMONG ELDERLY WOMEN FOUND TO APPROACH THAT OF THEIR MALE COHORTS

Epidemiologists now are seeing heart attacks as frequently among elderly women as among men. The increase stems in part from obesity and higher lipid levels, according to the director of the Framingham Heart Study.

"By age 60 every 17th woman has had a heart attack, and after that age the rate catches up with that of men, where half will have died of myocardial infarction, stroke, or some cardiovascular problem," Dr. William Castelli commented at the American Heart Association's 25th Annual Conference on Cardiovascular Disease Epidemiology.

He was responding to a paper presented by Elaine Eaker, ScD, from the National Institutes of Health in Bethesda, analyzing 30 year's of follow-up of coronary disease in women aged 50-59 from the Massachusetts study. Nothing had changed among the incidences of hard CHD endpoints, she reported, in the three decades since 1950. At the same time, CHD morbidity and mortality had decreased among men 50-59.

She itemized the risk factors as cigarette smoking, glucose intolerance, increased serum cholesterol—including increased LDL, decreased HDL, and an increase in the ratio of total serum cholesterol over HDL. "Menopause per se does not appear to be an independent risk factor for CHD. However, the effect of removing a woman's ovaries prior to the age of natural menopause must be examined in a population of women prior to the age of natural menopause.

"Across all three baseline exams women had significantly greater cholesterol levels than men, though the level has decreased for both sexes," Dr. Eaker said. "Thirty years' ago women had significantly higher systolic and diastolic blood pressure and greater relative weight than men, but they were less likely to have smoked cigarettes, or smoked fewer than did male counterparts. And by the 1970s women's blood pressures and relative weight were significantly lower than men's and a slightly greater portion of women were taking medication for high blood pressure."

By 1970, an equal number of women and men smoked cigarettes, and even though the number smoked per day more than doubled, these still amounted to fewer than those smoked by men, she added.

Among the overlaps of risk factors, Dr. Eaker pointed out that systolic blood pressure, serum cholesterol, and all are significant in each sex. The relationship is similar concerning smoking and serum cholesterol, but she pointed out that while glucose intolerance is a highly significant risk factor among women, it has no bearing on the incidence of heart disease among men.

Among things advocated by Dr. Eaker at the Tucson meeting were broader, more representative samples for analysis, and a study of the significance of greater glucose intolerance among women. "We must begin studying the epidemiology of coronary heart disease in women both to better understanding of the disease process in women" she said, "and to understand the large sex differential from coronary heart disease in the country."

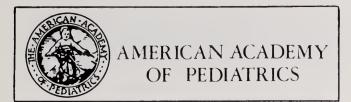
Dr. Castelli, looking at the signs, said that "we know lipids play a role. The LDL/HDL ratio is a highly significant sign of which women will get coronary heart disease, and triglycerides are an independent multivariate risk factor of some vascular problem."

The Framingham director observed that approximately one in 12 women will get strokes and it is known that blood pressure rises with age. "For every 10mmHg rise, the cardiovascular risk rises 30%, he added.

"Smoking is now one of the most important risk factors in women, where it was not in the 1950s and 1960s, before women learned to inhale. It is a top risk factor among women now—one of the top three."

The glucose intolerance factor also concerns Dr. Castelli. "It was a big thing in 1959, but the subsequent death rate from it has risen two percent. Obesity has always been another big factor, because it changes so many of the body's metabolic functions. Together, they explain the changes in heart disease patterns in the last 16 years, For example, lipids were not even considered a risk factor for the first 14 years. Diabetes, Type A behavior, lack of physical activity, also are very important.

"In other words, what we are doing is updating the awareness that, in fact, any woman undergoing an examination in the typical doctor's office who is heading for a heart attack or cerebrovascular event can be identified. The doctor could alter the outcome consoderably if he did his homework."



PROLONGED INFANT APNEA: AAP GUIDELINES SET

Prolonged infantile apnea, often defined as the cessation of breathing for at least 20 seconds, is a condition that some say might be linked to sudden infant death syndrome (SIDS).

However, since no causal relationship has yet been established and the etiology and optimal management of prolonged apnea are not clear, the American Academy of Pediatrics (AAP) Task Force on Prolonged Infant Apnea has issued guidelines to clarify which treatment can be implemented (e.g., monitoring technology) with available medicla knowledge.

Writing in the July issue of *Pediatrics*, the task force said infants who have had an episode of prolonged apnea are perceived by parents and physicians as "having experienced a life-threatening event and being at risk for another."

Prolonged apnea, they continued, can be a symptom of many disorders, including infection, seizure, airway abnormalities, hypoglycemia or other metabolic problems, anemia (in preterm infants), gastroesophageal reflux, impaired regulation of breathing during sleeping and feeding, and abuse.

The task force mentioned that prolonged apnea can also include a briefer episode of apnea associated with bradycardia, cyanosis or pallor. Brief episodes of apnea are a normal occurrence in infants, but prolonged apneic episodes may lead to morbidity—though rarely mortality.

To correct the emotional and sometimes erroneous information about apnea and SIDS, the task force voiced concern "that the vast majority of infants with prolonged apnea are not victims of SIDS; most SIDS victims were never observed to have had prolonged apnea prior to the terminal event."

They did say, however, that there is an indication that preterm infants as a group and perhaps siblings of infants who were victims of SIDS are at somewhat increased risk.

To update 1978 recommendations from a similar AAP task force, the present group emphasized the following major points regarding prolonged apnea:

- 1) Physicians must be responsible for all evaluations and management of infants with prolonged apnea.
- 2) A thorough initial evaluation to determine possible treatable causes of apnea is mandatory.
- 3) Asymptomatic infants, including those with previous apnea or those with statistically increased risk of SIDS, may be candidates for home monitoring, but there are no tests that will reliably determine risk status. Physicians should prescribe monitorin if they feel that method of management is in the best interest of their patient.

- 4) Monitoring technology is still being developed and refined. Most authorities feel that both cardiac and respiratory functions should be monitored electronically. Some feel monitoring cardiac function alone is equally effective. Ability to produce a permanent record, when needed, is desirable.
-) When home monitoring is elected, parents should be advised that monitors cannot guarantee against SIDS. Monitor advertisements that assure absolute protection should be condemned for unscrupulous attempts to profit from the situation. A plan for periodic re-evaluations and termination of monitoring should be developed and explained to the parents.
- 6) Because the etiology and optimal management of prolonged apnea are not clear and because a causal relationship between prolonged apnea and SIDS has not been established, continued research is essential.

DENIM DILEMA: JEAN SEAMS AND TAILBONES

Two case studies reported by child health professionals in Cleveland note a denim dilema: tight jeans and their seams causing low back pain.

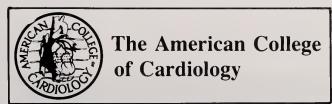
Writing in the July issue of *Pediatrics*, Edward Mortimer, M.D., and Marcie Stoshak, from the Department of Pediatrics at Cleveland's Case Western Reserve University, give some practical advice on an offbeat adolescent problem.

The first case involved a 14-year-old female student who complained of low back pain and tenderness for two months (since she had returned to school in September). On examination, there were no findings but the location of the pain was determined to be the coccyx (tailbone).

On questioning, the young woman acknowledged wearing tight jeans with heavy reinforced seams to school. Recommendation: avoid wearing the jeans and try to sit in a more erect position on the hard school seats. Verdict: three weeks later the pain and tenderness disappeared after she complied.

In another case, a 16-year-old female student was initially seen with a similar complaint that had been present the previous year. Symptoms disappeared during the summer, but returned upon the start of school. Examinations and medical tests were negative except for coccygeal tenderness. Her school attire was similar to the first case, so the same treatment was prescribed. The symptoms promptly went away.

Dr. Mortimer and Ms. Stoshak concluded that the recognition of this problems by physicians could prevent needless medical tests.



FONTAN PROCEDURE FOR TRICUSPID ATRESIA SHOWN TO HAVE LONG-TERM EFFECTS

Patients Treated by the Fontan procedure for tricuspid

atresia have maintained the benefit they received from the procedure for as long as 16 years, according to a follow-up study by an Indianapolis cardiologist.

The Fontan procedure has become the "surgery of choice" for treating many children and some adults with this congenital heart defect, reports Dr. Donald A. Girod, M.D., professor of pediatrics, Indiana University Medical Center. The procedure has long-term efficacy.

"This is further reassurance that it is proper to do the Fontan procedure in properly selected patients", he says.

Dr. Girod reported on his evaluation of 28 of the earliest patients of the procedure's developer, Francis Fontan, M.D., during Wednesday's original contribution session on "Postoperative Evaluation Following Surgery for Congenital Heart Disease". These patients were followed for 7-16 years, longer than in any previous study.

Tricuspid atresia patients generally begin having serious problems by their late teens or early 20s, Dr. Girod said. Some may continue to do well, but their normal pattern is to decline. In contrast, Fontan patients, while not free of complications, maintained their symptomatic improvement over the period of this study.

The Fontan procedure radically alters circulation; it reroutes systemic venous blood directly from the right atrium to the lungs. The method has become popular and is used in many specialty cardiac surgery centers in the U.S. to treat hundreds of patients.

This study allays some of the concern about this procedure's possible long-term effects, he says. Some cardiologists have worried, because of its radically changed circulation, that the patients could develop liver damage, left ventricular dysfunction or arrythmias.

"We didn't find evidence that these problems interfered with good long-term results in most patients," Dr. Girod says.

Previous studies have shown that these patients do well immediately after surgery. Their cyanosis is eliminated. Almost all can exercise more. Most can do low-grade exercise but, for the most part, cannot do competitive exercise.

The oldest patient was 36 at the time of surgery, has been followed for 15 years, is now 51 and gave birth to a healthy infant 3 years after the surgery.

Many of these patients had been treated previously by the shunt operation, which generally leaves patients with "significant impairment in exercise tolerance," he says. The Fontan procedure, which generally has replaced or follows the shunt operation, gives better symptomatic improvement.

Many patients, particularly those younger than 4-5 years, still receive the shunt operation.

In-hospital mortality ranges from about 2-10 percent depending on various risk factors.

DILTIAZEN MAY BE CALCIUM BLOCKER OF CHOICE FOR PATIENTS ON CONCURRENT CHRONIC DIGOXIN

Diltiazem is preferable to other calcium channel blockers in patients concurrently receiving chronic

digoxin treatment, according to new data.

In a study by Dr. Uri Elkayam and a team from the University of Southern California School of Medicine, diltiazem—in doses up to 240mg per day— did not alter digoxin serum concentration or renal clearance in patients being treated for heart disease.

"Diltiazem is becoming more widely used in the management of ischemic heart disease, arrhythmias, and systemic hypertension," Dr. Elkayam, Associate Professor of Medicine, told an audience attending the 34th Annual Scientific Session of the American College of Cardiology. "Many patients who benefit from using this drug are also treated with digoxin. Thus, interation between these two agents has obvious clinical significance."

Other calcium channel blockers have been found to have "clinically significant" interactions with digoxin, he said. In fact, in a recent study, the addition of verapamil to digoxin caused a significant decrease in digoxin renal clearance. Furthermore, digoxin toxicity occurred in some patients in whom the digoxin serum concentration was increased.

In Dr. Elkayam's trial, nine patients ranging from 34 to 66 years of age were selected for evaluation with diltiazem. All had been undergoing chronic therapy with a daily dose of digoxin, 25mg, for either supraventricular arrhythmias or heart failure. Patients who had been receiving other cardiac drugs continued those medications throughout the study.

Digoxin serum concentrations were measured at the beginning of the study and 4-7 days after the start of diltiazem, 120mg/day given in four divided doses. Digoxin serum concentrations were also determined 5-20 days after the diltiazem dose had been increased in 240mg/day, again in four divided doses.

Digoxin renal clearance was measured at control and repeat measurements were taken while patients were receiving diltiazem, 24mg/day.

"Serum digoxin concentration increased by 33% from 0.6 to 0.8 ng/ml in one patient," Dr. Elkayam explained. "All other patients, however, failed to demonstrate a substantial change in serum digoxin concentration during diltiazem therapy."

A 30% change in renal digoxin clearance occurred in one patient when diltiazem was added to digoxin therapy, but there was no change in dogoxin serum concentration in that patient. Roughly half the remaining patients had a small increase in digoxin clearance and half had a small decrease. Overall, said Dr. Elkayam, the changes in values at control and during therapy were insignificant.

Because digoxin serum concentrations and digoxin clearance are unchanged when diltiazen is added to long-term digoxin therapy for heart failure, diltiazem (rather than verapamil) should be used when a calcium channel blocker is required, Dr. Elkayam concluded.

Dr. Elkayam is also Director of Inpatient Cardiology at the USC School of Medicine. His colleagues in the present work were Laura Weber, RN, and Drs. Arie Roth, Willa Hsueh, and Shahbudin Rahimtoola.

ORAL ACEBUTOLOL PREVENTS SUPRAVENTRICULAR TACHYARRHYTHMIAS IN PATIENTS WITH CABGS

Oral acebutolol can help prevent supraventricular tachyarrhythmias after coronary artery bypass surgery, a French group has found.

The investigators caution, hovever, that it has not yet been established whether or not acebutolol is more effective than other beta blockers in this regard. Acebutolol is a cardioselective beta blocker with moderate intrinsic sympathomimetic activity.

The present study was conducted by Drs. Patrick Daudon, Iradj Gandjbakhch, Thierry Corcos, Annick Cabrol, and Christian Cabrol from the Hospital de la Pitié in Paris. These investigators found that supraventricular tachyarrhythmias developed in 40% of patients in a control group within the first eight days after bypass surgery but in none of the acebutolol-treated patients.

In a presentation to the 34th Annual Scientific Session of the American College of Cardiology, Dr. Corcos reported that one hundred patients from 30 to 77 years of age were included in their study. Patients with left ventricular aneurysm and preoperative arrhythmias were excluded. Patients in whom beta blockers were contraindicated were also ineligible.

Thirty-six hours after surgery, 50 patients were randomized to oral acebutolol given twice daily until discharge. Patients were started on a 200 or 400mg dose depending on their weight, after which the dosage was adjusted to maintain a resting heart rate o approximately 70 beats per minute, Dr. Corcos said.

Fifty control patients were not treated with beta blockers after surgery. The two groups were similar in terms of a number of clinical descriptors including sex, angina functional class, ejection fraction, number of diseased coronary vessels, number of bypass grafts, and duration of cardiopulmonary bypass. Continuous and daily ECGs were obtained in all patients and 24-hour Holter monitoring records were obtained in the last 20 patients.

Seventeen (34%) of the control patients developed atrial fibrillation and 3 (6%) had atrial flutter, with the majority of these events developing within the first three days after surgery. There were no cases of paroxysmal atrial tachycardia.

None of the acebutolol-treated patients had a supraventricular tachyarrhythmia.

"Several studies have shown beta blockers, and particularly propranolol, to be effective in reducing the incidence of postoperative supraventricular tachyarrhythmias," Dr. Corcos said, "but a recent study...did not show any significant reduction in postoperative arrhythmias in the propranolol-treated group." Dr. Corcos also cited a study showing that timolol, given prophylactically, reduced the incidence and severity of supraventricular tachyarrhythmias after bypass surgery, although at least one bout of supraventricular tachyarrhythmias did occur in all patients, treated or not.

Nonetheless, Dr. Corcos said, the results of the present study indicate that oral acebutolol "can be recommended as a standard therapeutic regimen" for preventing supraventricular tachyarrhythmias after bypass surgery.

Dr. Corcos said that supraventricular tachyarrhythmias are extremely common after bypass surgery and may, in part, result from abrupt discontinuation of beta blockade. [Another study has shown that abrupt withdrawal of beta blocker during myocardial infarction does not have deleterious effects. See report on the work of C.H. Croft and his group, next issue.] "Urgent" drug therapy or cardioversion may be required in some patients, he said.

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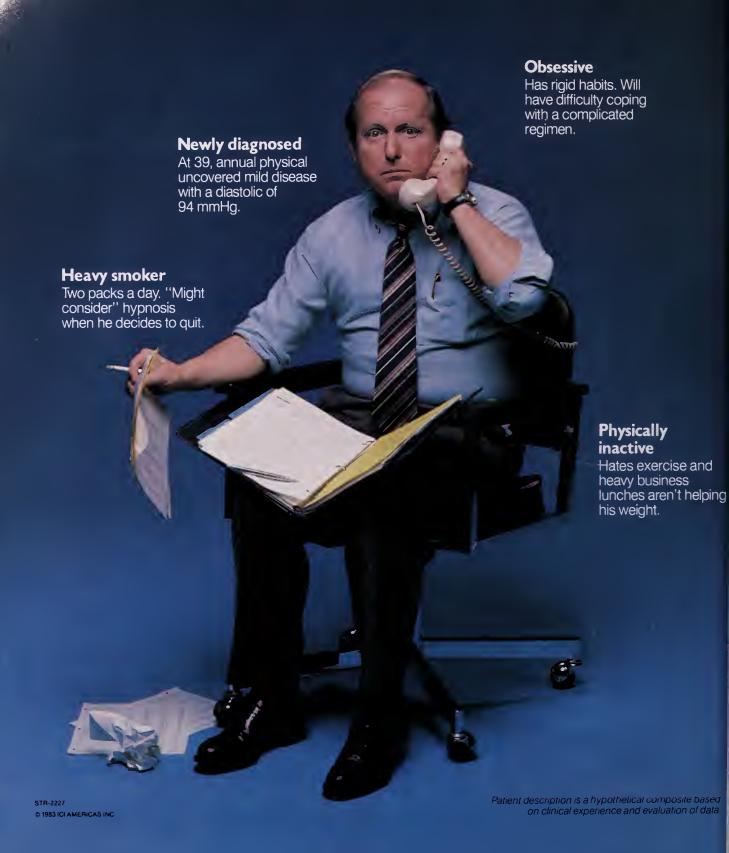
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What can you do for hypertensives like Paul H?



Rely on one-tablet-a-day dosage and cardioselectivity.

"Real life" efficacy

Paul H represents 2,514 men under 40 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even Paul H's age group.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Lessens risk of bronchospasm

Propranolol may produce bronchial hyperactivity in patients with no history of asthma. Reasons for this are not fully understood, but smoking has been implicated especially in males like Paul H. TENORMIN exerts a preferential effect on cardiac (β_1) receptors rather than on bronchial or peripheral (β_2) receptors. Although this preference is not absolute, wheezing and shortness of breath seldom occur.

See following page for brief summary of prescribing information.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁵ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



For Paul H...and virtually all your hypertensive patients

TENORMIN® (atendol)



For Paul H... and virtually all your hypertensive patients

TENORMIN* (atenolol) A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN* (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide. 4-[2'-hydroxy-3'-[(1-methylethyl) amino] propoxy]- Alenolol (free base) has a molecular weight of 266 it is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37° C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/ml at 25° C)

and less soluble in chloroform (3 mg/ml at 25°C)
INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS). WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further

function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction. In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TENORMIN therapy should be withdrawn. Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectors and, in some cases, myocardial infaction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overlangina pectors, when discontinuation of TENORMIN is planned, the patient should be cardival beserved and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withshould be advised to limit physical activity to a minimum. TENORMIN should be reinstated if with-

should be advised to limit physical activity to a minimum. TENORMIN should be reinstated it withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN
GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do
not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is
not absolute the lowest possible dose of TENORMIN should be used, with therapy Intilated
at 50 mg and a beta,-stimulating agent (bronchodillator) made available. If dosage must be
increased, dividing the dose should be considered in order to achieve lower peak blood

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to

levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia if treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene. TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg., dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg., profound bradycardia, hypotension) may be corrected with atropine (1-2 mg I.V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg., tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg., reserpine) may have an additive effect when given with beta-blocking agents Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycarda which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients rec

of clondine

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of vanous mutagenicity studies support this finding

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuulation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all lested dose levels of atenoiol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenoiol/kg/day(150 and 75 times the maximum recommended human dose,

USAGE IN PREGNANCY: Pregnancy Category C Atenolof has been shown to produce a doserelated increase in embryo / tetal resorptions in rats at doese equal to or greater than 50 mg /kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg /kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORNIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenolol

Pediatric Use: Safety and effectiveness in children have not been established ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U.S. studies) or elicited (eg. by checklist—foreign studies). The reported frequency of eli-cited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were voluntee is similar, causal relationship is uncertain

The following adverse-reaction data present frequency estimates in terms of percentages. first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered side effects).

from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects)

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%), leg pain (0%-0.5%), leg pain (0%-0.5%), leght-headedness (1%-0%), tredness (0.6%-0.5%), latigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0.9%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL diarrhea (2%-0%), nausea (4%-1%)

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCUL AR Pardycardia (3%-0%), cold extremities (12%-5%), postural hypotension.

TOTALS U.S. AND FOREIGN STUDIES:
CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-19%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR. dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), tiredness (26%-13%), latique (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-19%)
GASTROINTESTINAL diarrhea (3%-2%), nausea (3%-19%)
RESPIRATORY (see WARNINGS) wheeziness (3%-3%), dyspnea (6%-4%)
MISCELLANEOUS. There have been reports of skin rashes and /or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

fored following cessation of therapy

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported
with other beta-adrenergic blocking agents, and may be considered potential adverse effects of
TENORMIN (atenolol).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by discrientation of time and

bances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia. Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practicol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practicol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia

bronchospasm, and hypoglycemia in the case of overdosage, treatment with TENORMIN should be stopped and the patient care-fully observed TENORMIN can be removed from the general circulation by hemodialysis in addi-tion to gastric lavage, the following therapeutic measures are suggested if warranted Bradycardia: Atropine or another anticholinergic drug Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker. Congestive Heart Fallure: Conventional therapy Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or nor-epinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Aminophylline, isoproterenol, or atropine

Hypoglycemia: Intravenous glucose
DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to duretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including

thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 ml/min/173 m² (normal range is 100-150 ml/min/173 m²), therefore, the tollowing maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (ml/min 1 73 m²)	Elimination Halt-lite (hrs)	Maximum Dosage		
15-35	16-27	50 mg daily		
<15	>27	50 mg every other day		

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolot) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets of 100 mg TENORMIN (atenolot): round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets. Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

temperature

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Resumenes de La Literatura 7 VI édica

THE EFFICACY OF INFECTION SURVEILLANCE AND CONTROL PROGRAMS IN PREVENTING NOSOCOMIAL INFECTIONS IN U.S. HOSPITALS. Haley RW, Culver DH, White JW, Morgan WM, Emori TG, Munn VP, Hooton TM. Am J Epidemiol 1985; 121:182-205

En una muestra representativa de los hospitales generales de Estados Unidos, los autores encontraron que el establecimiento de programas intensivos de vigilancia y control de infecciones estaba fuertemente asociado con reducciónes en las tasas de infecciones urinarias nosocomiales, infecciones quirúrgicas, pulmonía y bacteremia, entre 1970 y 1975-76, aún controlado por otras características de los hospitales y sus pacientes. Los componentes esenciales de los programas efectivos incluían llevar a cabo actividades organizadas de vigilancia y de control, y tener un médico efectivo y entrenado en el control de infecciones, una enfermera/o de control de infecciones por cada 250 camas, y un sistema para notificar a cada cirujano las tasas de infecciones quirúrgicas en sus pacientes. Los programas con estos componentes redujeron las tasas de infección en sus hospitales por un 32%. Sin embargo, como relativamente pocos hospitales tenían programas muy efectivos, sólo el 6% de las (aproximadamente) 2 millones de infecciones nosocomiales en la nación estaban siendo prevenidas en la mitad de la década de los 70, dejando otro 26% que hubieran podido ser prevenidas mediante la adopción universal de estos programas. En los hospitales sin programas efectivos, la tasa general de infecciones aumentó un 18% entre 1970 y 1976.

El "Study on the efficacy of nosocomial infection control", tomó 10 años en completarse. De nuevo, para un programa efectivo de control de infecciones nosocomiales los elementos necesarios son: llevar a cabo actividades organizadas de vigilancia y de control, tener un médico efectivo y entrenado en el control de infecciones, una enfermera/o de control de infecciones por cada 250 camas, y un sistema para notificar a cada cirujano las tasas de infecciones quirúrgicas en sus pacientes. Será dificil que el "Joint Commission for Hospital Accreditation" no incorpore a sus exigencias los hallazgos de un estudio tan meticuloso y respetado como éste.

J.G. Rigau-Pérez, M.D., F.A.A.P.

IDENTIFYING PATIENTS AT HIGH RISK OF SURGICAL INFECTION: A SIMPLE MULTIVARIATE INDEX OF PATIENT SUSCEPTIBILITY AND WOUND CONTAMINATION. Haley RW, Culver DH, Morgan WM, White JW, Emori TG, Hooton TM. Am J Epidemiol 1985; 121:206-15

Un sistema muy sencillo para clasificar los pacientes quirúrgicos ha sido presentado recientemente por el mismo grupo de investigadores que llevó a cabo el SENIC. Los pacientes se categorizan según un índice de riesgo que tiene cuatro variables, con valor de 0 ó 1, si la variable está ausente o presente. Las variables son: operación abdominal, operación de más de 2 horas de duración, operación clasificada como contaminada o sucia-infectada, según el sistema tradicional de clasificación de operaciones, padecer 3 ó más condiciones diagnosticadas en el récord. De esta manera, cada paciente puede tener un índice desde 0, si no tiene ninguna de las variables, hasta 4, si las tiene todas. El estudio encontró que los pacientes con un índice de 4 tenían un riesgo de infección 27 veces mayor que los pacientes con índice de 0.

Un sistema como éste permite dirigir la vigilancia a los pacientes de bajo riesgo, donde no deben ocurrir infecciones. Por el otro lado, para economizar recursos, se podría vigilar preferentemente a los pacientes de alto riesgo, que en el estudio citado eran la mitad de los pacientes quirúrgicos pero tenían el 90% de las infecciones. Un sistema así también haría posible la comparación de tasas de infección entre diferentes hospitales.

J.G. Rigau-Pérez, M.D., F.A.A.P.

EL DRENAJE PERCUTANEO EXITOSO EN QUISTE HIDATIDICO DEL, HIGADO Mueller PR et al Radiology 1985; 155: 627-628

La aspiración del quiste hidatídico del hígado ha sido tradicionalmente evitada debido a las complicaciones potenciales tales como shock anafiláctico y la diseminación de quistes al peritoneo. Los autores de este articulo usaron con éxito el drenaje percutáneo de un quiste hidatídico en una paciente con quiste recurrente. Con control radiográfico el quiste fue drenado y luego lavado

con una solución de nitrato de plata y salina hipertónica. Un año después de este drenaje, las funciones hepáticas permanecían normales en la paciente. Aún cuando el drenaje quirúrgico es el método de preferencia en quistes hepáticos por equinococo, el drenaje percutáneo por cateter puede ser una alternativa en pacientes de alto riesgo quirúrgico.

Bernardo Marqués, M.D.

TRATAMIENTO AMBULATORIO DE ABSCESOS INTRAABDOMINALES LUEGO DE DAR DE ALTA A LOS PACIENTES TEMPRANAMENTE Riefkin MD, et al Radiology 1985; 155:333-334

Aunque el drenaje percutáneo de abscesos intraabdominales frecuentemente evita cirugía abierta, los pacientes permanecen hospitalizados frecuentemente durante el drenaje. Los autores trataron a nueve pacientes con abscesos intraabdominales usando el drenaje percutáneo y enviaron a los mismos a sus casas con el cateter de drenaje in situ. Todos recuperaron sin problemas. Este procedimiento ahorró aproximadamente \$12,050.00 en cada caso. Los autores sugieren que el continuar el drenaje de abcesos intraabdominales ambulatoriamente es mucho más económico que el tratamiento dentro del hospital y no conlleva riesgo mayor para el paciente.

Bernardo Marqués, M.D.

RESPIRATORY REHABILITATION IN SEVERE RESTRICTIVE LUNG DISEASE SECONDARY TO TUBERCULOSIS. Yang GFW, Alba A, Lee M. Arch Phys Med Rehabil 1984; 65:556-558

Este artículo presenta el caso de una mujer hispana de 44 años con insuficiencia respiratoria crónica a quien se le facilitó el uso de aparatos portátiles para su tratamiento. La paciente tenía enfermedad pulmonar restrictiva severa secundaria a amagullamiento del nervio frénico/ pneumoperitóneo/decorticación por tuberculosis de lóbulo inferior bilateral. En 1969, 12 años después de la última operación, desarrolló coriza, disnea y somnolencia. Se hospitalizó y presentó gases arteriales sanguíneos con PaO2 de 30 mmHg, PaCO2 de 77 mmHg y un pH de 7.28. Las pruebas de función pulmonar eran compatibles con hipoventilación alveolar. Desde 1969, la paciente empezó a usar el ventilador poncho, ("wraparound") para su cuidado respiratorio a largo plazo. En 1971, descubre que la ventilación por presión intermitente por boca (MIPPV), usualmente utilizado por pacientes con desórdenes neuromuculares, es más sencilla. Desde entonces, ella ha estado usando un respirador Bantam con MIPPV y un guarda-labios/pieza de boca durante la noche, y el respirador y guarda-labios por unas pocas horas al día. Cuando la paciente padece infección respiratoria o está cansada, encuentra mayor comodidad

usando el poncho. Con la ayuda de estos 2 aparatos respiratorios, esta paciente ha completado su educación, está casada y ha llevado una vida exitosa.

Mabel Cabán, M.D.

IN-HOSPITAL EXERCISE THERAPY IN
PATIENTS WITH SEVERE ANGINA PECTORIS.
Stubbe I, Gustafson A, Nilsson-Ehle P,
Agren B. Arch Phys Med Rehabil
1983; 64:396-401

The authors evaluated the physiologic, psychologic and metabolic effects of a nine-week inhospital training program on 14 men with severe disabling angina pectoris. The exercise program consisted of intensive internal training on an ergometer bicycle for two 30 minute sessions daily. The physical performance increased by about 40%. Plasma insulin levels were reduced and glucose tolerance test improved significantly. There was a decrease in plasma triglyceride and low density lipoprotein cholesterol levels, but no change in high density lipoprotein cholesterol and apoliporotein A1 and B concentrations. Plasma triglyceride and low density lipoprotein remained low three weeks after completion of the training period and the physical performance remained improved even six months post training. Four of the patients who had been disabled for at least five months were able to return to work. The authors suggest that comparatively short and intensive inhospital rehabilitation of patients with coronary heart disease may be an attractive alternative to prolonged training on an outpatient basis, especially in patients with severe angina pectoris.

José R. Busquets, M.D.

SOCIOS NUEVOS



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INTERNO-RESIDENTE

Sánchez Longo de León, Isis M., MD - Escuela de Medicina de la Universidad Católica Madre y Maestra, República Dominicana, 1982, Psiquiatría.

REINGRESO

Portela García, Jesús, MD - Universidad de Madrid, España, 1959, Medicina de Familia. Ejerce en Houston, Texas.

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LONG-TERM USE OF COCAINE MORE DEADLY THAN HEROIN

Cocaine, when used regularly for prolonged periods, may be more lethal than heroin. The finding comes from a study of the effects on laboratory rats that self-administered unrestricted amounts of both drugs.

During the 30-day study period, 23 rats had continuous access to either intravenous cocaine hydrochloride (12), or heroin hydrochloride (11). Michael A. Bozarth, PhD, and Roy A. Wise, PhD, of Concordia University, Montreal, Canada, measured the rats' hourly drug intake for each 24-hour period of testing, and made observations concerning the general health of all the animals. Although all the rats learned to self-administer the drugs, there were differences in patterns of use: those receiving heroin showed stable use, with gradual increase during the first two weeks; those receiving cocaine used it erratically, with excessive use alternating with brief periods of abstinence.

"The general health of the animals became markedly different," the researchers say. "Those self-administering heroin maintained good grooming behavior, pretesting body weight, and a good state of general health; rats self-administering cocaine tended to cease grooming behavior, to lose up to 47 pecent of their pretesting body weight, and to show a pronounced deterioration in general health." The researchers say the mortality rate for the 30 days of testing was 36 percent for rats self-administering heroin and 90 percent for those self-administering cocaine.

"These results suggest that cocaine is a much more toxic compound than heroin when animals are given unlimited access to intravenous drug," the researchers conclude. They suggest that the limited availability and relatively low purity of cocaine may account for the relatively few deaths associated with its use in human populations.

In a related article, Russell E. Howard, MD, and colleagues of Northwestern University Medical School, Chicago, describe the case of a previously healthy 28-year-old woman who suffered a heart attack several hours after sniffing cocaine. Although the report provides no direct evidence of a cause-effect relationship, the researchers say this occurrence should alert the

medical community to the possibility that some persons without underlying heart disease may be at risk for myocardial infarction when exposed to cocaine.

Commenting editorially, William Pollin, MD, Director of the National Institute of Drug Abuse, Rockville, Md., says recent data indicate a 91 percent increase in cocaine-related deaths from 1980 through 1983 in the United States. He adds, "Whether or not there has been a recent increase in the number of cocaine users in this country, it is clear that more intensive and destructive patterns of use—including freebasing, intravenous administration, and the use of cocaine in combination with drugs—have occurred among the existing population of users."

Pollin says until recently cocaine was thought to be a relatively innocuous, nonaddicting substance, and that was one reason its use spread so quickly, especially among those who were able to afford its high price. "Cocaine is now becoming widely recognized as one of the most dangerous illicit drugs in common use," he says, adding that the Bozarth and Wise article provides a piece of useful evidence for physicians in educating their patients.

JAMA July 5, 1985

BASIC SKILLS NEED EMPHASIS, RECENT RESIDENT PHYSICIANS REPORT

More training in basic skills, including history—taking and physical examination, is needed in residency programs, say recent graduates in a survey published in JAMA. Less drilling in certain technical procedures also would improve medical training for "real world" practice, surveyed physicians add.

Conducted by Donald C. Kern, MD, MPH, and colleagues from Boston University School of Medicine, the study was aimed at strengthening the school's residency program in internal medicine. Surveyed were 61 recent graduates, 56 of whom responded to a detailed questionnaire. At issue was the difference, if any, between training received and skill sets used in real-world practice.

Among survey findings: 95 percent of the physicians were board certified; 80 percent had subspecialty training; and 89 percent provided direct patient care. Of the many topics reviewed, 56 showed disparity between preparation and importance scores. For 14 categories, mainly technical procedures, disparate ratings suggested excessive programmatic emphasis, while for 42 categories there may have been inadequate emphasis.

"As a group, basic skill and knowledge areas (e.g., history taking, physical examination and interpersonal skills) received the highest scores for importance," the researchers say. "In contrast, the ratings given to most technical procedures would suggest that their value declines with time. The declining value of many technical skills may reflect their short 'half life,' and be an indication that some should be deemphasized in relation to

other knowledge and skill areas."

The surveyed physicians had begun their residency programs at Boston University between 1973 and 1977 and were questioned in 1982.

"This study examines program content in the light of real-world demands made on practicing internists," the researchers say. "It indicates that, if internists are likely to practice primary care or general internal medicine, regardless of their subspecialty status, more emphasis on the basic skills required to practice general medicine is necessary," they conclude.

JAMA July 5, 1985

URINARY TRACT INFECTIONS RELATED TO DIAPHRAGM USE

Women who use diaphragms as a contraceptive method have twice the risk for contracting urinary tract infections (UTIs) as women using the pill, according to a report in JAMA.

Stephen D. Fihn, MD, MPH, of the University of Washington, Seattle, and colleagues conducted two separate studies to determine whether there was an association between UTIs and diaphragm use. The first study included 199 women who used various contraceptive methods and who had UTIs (114 cases) or other genitourinary symptoms (85 controls). The second study followed the incidence of UTI during a 9.4 month period in 192 diaphragm users and in 182 women taking oral contraceptives.

"Both studies demonstrated a significantly increased risk of UTI in diaphragm users," the researchers say. "Relative odds were 2.0 in the case-control study and the risk was 2.5 in the retrospective cohort study." They add that this increased risk could not be attributed to differences in age, parity, sexual activity or previous UTI.

In the case-control study, 57 (50 percent) of the 114 women with UTIs currently used diaphragms, compared with only 28 (33 percent) of 85 who did not have such infections. The study also revealed that diaphragm users had more UTIs within the prior six months. In the retrospective cohort study, 34 (21 percent) of 165 diaphragm users developed UTIs compared with 14 (9 percent) of 148 women taking oral contraceptives. (Sixty-one women had switched contraceptive methods and were studied separately).

The researchers note that evidence from other studies supports their findings. They conclude, "Our results suggest, but do not prove a causal relationship between diaphragm use and UTI." Possible causes include partial obstruction of the urethra and changes in the normal vaginal flora from diaphragm and/or spermicide use. Until these causes are elucidated, however, the researchers suggest that women who use diaphragms and have recurrent UTIs may want to change contraceptive methods, but that potential benefits of diaphragm use, such as protection from cervicitis and salpingitis should also be considered.

JAMA July 12, 1985

EXPORTING SALMONELLA VIA PET TURTLES: STUDY

The estimated 3 to 4 million pet turtles exported from the United States each year are an important route for the transmission of salmonellosis, according to a report in JAMA.

Robert V. Tauxe, MD, MPH, of the Centers for Disease Control, Atlanta, and colleagues base their conclusion on a case-control study of salmonellosis in Puerto Rico. The researchers note that commercial distribution of turtles less than 4 inches long within the United States was banned in 1975 by the Food and Drug Administration, but in 1983 the pets were still being exported to many countries, including Puerto Rico.

Extensive interviewing of individuals or families for 83 reported cases of salmonellosis and 83 matched controls enabled the researchers to determine risk factors for infection from food, water, animals or other sources. They report that 60 cases occurred in children younger than 1 year, and ten of these were associated with pet turtles. For the 23 older children and adults, no significant associations with risk factors for salmonellosis were noted, but two of these case patients were also exposed to pet turtles before onset of illness.

Turtles from 18 pet shops in Puerto Rico were then cultured in lots. All 18 were positive for at least one type of Salmonella; Salmonella pomona appeared in 89 percent of the lots. The researchers note that this strain has also been found in pet turtles exported from the United States to Guam and Yugoslavia, and other strains have been isolated from turtles exported to Japan and the United Kingdom. In 1983, more than 1 millon turtles were exported from New Orleans to Japan; France, Italy and Hong Kong received about 200,000, and smaller numbers went to other European, Latin American and Eastern countries.

"In Puerto Rico, pet turtles accounted for 12 to 17 percent of cases of salmonellosis in infants reported in 1983," the researchers say. They note that the actual incidence may be much higher, since in the U.S. only an estimated 1 percent of all salmonella infections are reported. "If this estimate is applied to Puerto Rico, there may actually have been one turtle-associated human infection for every 10 turtles shipped in 1983."

The worldwide incidence of Salmonella infections has been increasing, the researchers say, and contamination of food such as raw meat is often difficult to control. "Some vehicles of salmonellosis, such as imported pet turtles and unpasteurized milk, however, can be easily and inexpensively controlled by appropriate regulation," they observe.

Commenting editorially, Eugene J. Gangarosa, MD, of Emory University School of Medicine, Atlanta, says it is incongruous that there are effective controls to prevent export of products affecting national security, but no constraints on export of products that effect health. He says that for many items, including turtles, existing regulations do not even prohibit exports to countries that

have banned their importation.

Gangarosa says it is our responsibility as a nation to attempt to protect children in other countries from products we know to be dangerous. He adds that in this case, negligence may permit Salmonella to return to the United States through imported foodstuffs or as a result of travel. "What are urgently needed are export constraints in the United States so that people of distant lands are protected against pet turtles and other knowingly dangerous products we export, which include but are not limited to pesticides, obsolete pharmaceuticals and toxic wastes." Gangaroa notes that the United States was the only country to vote against a 1979 United Nations resolution urging member states to exchange information on hazardous chemicals and to discourage exportation of such products.

JAMA July 12, 1985

DEPRESSION, DRUGS PREVAIL IN CITIES: STUDY

Major depressive episodes and drug abuse are more common in urban areas, while alcohol abuse is more common in rural areas, according to a survey of 3,921 adults that appears in the July Archives of General Psychiatry. Conducted by Dan Blazer, MD, PhD, of Duke University Medical Center in Durham, N.C., and colleagues, the study compared psychiatric disorders of urban and rural patients living in the Piedmont area of North Carolina. When disorders were stratified for age, sex, race and education (to control confounding factors), "major depressive disorders were found to be twice as frequent in the urban area," the researchers say.

PREVALENCE OF PARKINSON'S LOWER IN CHINA

The prevalence of Parkinson's disease in the Peoples' Republic of China is markedly lower than in European or North American countries, according to a study in the July Archives of Neurology. Shi-chuo Li, MD, of the Beijing Neurosurgical Institute in China, and colleagues report on a six-city survey of 63,195 individuals aimed at assessing neurological disorders. They found that the prevalence ratio for Parkinson's was 57 per 100,000 population. Ratios for western countries range from 65 per 100,000 to 187 per 100,000. Different criteria for diagnosis and classification, different levels of case ascertainment, and differences in the demographic features of the population could account for the numerical discrepancies, the researchers say.

ASPARTAME DEEMED SAFE FOR HEALTHY INDIVIDUALS

The nutritive sweetener aspartame is a safe sugar substitute for normal humans, according to an AMA Council on Scientific Affairs report appearing in JAMA. "Available evidence suggests that consumption of

aspartame is safe expect by individuals with homozygous phenylketonuria (a rare metabolic disorder that can cause mental retardation) or other individuals needing to control their phenylalanine intake," the council report says.

When approving the substance for use in soft drinks, the Food and Drug commissioner concluded that maximum projected consumption of aspartame by normal children and adults was far, far below any level even suspected of being toxic, the report points out.

In addition, the Centers for Disease Control has cleared the substance of any association with serious adverse health effects, the report says. Recently, the CDC evaluated complaints related to consumption of products containing aspartame. The CDC conducted interviews with 517 complainants and reported that the great variety of complaints were mild in nature.

"Although it may be that certain individuals have an unusual sensitivity to the product, these data do not provide for the existence of serious, widespread, adverse health consequences attendant to the use of aspartame," the CDC concluded. Questions had been raised about the possibility that aspartame, alone or in combination with glutamate, might contribute to brain damage, the council points out. Another fear was that aspartame might induce brain tumors in laboratory rats. Studies in humans cleared the substance of the first question, and two-year studies involving three distinct rat populations cleared the substance of the second fear.

Aspartame is 180 to 200 times sweeter than sucrose, so very small amounts are needed to achieve equivalent sweetness, the council says. "Individuals who need to control their phenylalanine intake should handle aspartame like any other source of phenylalanine," the council concludes. Others need not worry about adverse health effects.

JAMA July 19, 1985

CHILDHOOD OBESITY KEY TO HIGH CHOLESTEROL PROFILE

Susceptibility to heart attack can be detected in children as young as 12 years old, suggests a new study appearing in JAMA. Researchers from Louisiana State University Medical Center in New Orleans tracked 1,598 youngsters from ages 5 to 12 and found that increases in obesity in youth are accompained by an increasingly atherogenic lipoprotein profile.

Measured were increases in triceps skin-fold thickness, the muscle and flesh directly below the biceps in the arm, in relation to changes in total blood cholesterol, blood triglycerides, and low- and very low-density lipoprotein cholesterol, elevations of which are associated with increased risk of heart disease. Findings demonstrated "significant positive correlations" between increases in triceps thickness and elevations in blood lipids associated with heart disease.

"Although females showed the largest increases in triceps skin-fold thickness, most associations were stronger in males," report David S. Freedman, PhD, and colleagues.

"Obesity-related changes in serum lipids and lipoprotein levels during childhood may play a role in the initiation of atherosclerosis," they observe. "In adolescents and young adults, total cholesterol and low-density lipoprotein cholesterol levels are strongly related to aortic fatty streaks, and very low-density lipoprotein levels are associated with fatty streaks in the coronary arteries."

They point out that intervention programs among adults demonstrate a positive association between weight loss and reduction of heart disease risks, measured by changes in blood lipids. "Since the effects of weight loss on cardiovascular disease risk factors may be greater in younger than in older individuals, effective cardiovascular disease intervention should focus on prevention of excessive weight gain in childhood and adolescence, the researchers conclude.

JAMA July 26, 1985

RIFAMPIN EFFECTIVELY CONTROLS SPREAD OF DAY-CARE MENINGITIS

Spread of *Haemophilus influenzae* type b (Hib), the most common cause of bacterial meningitis in the United States, can be checked in day-care centers by administration of rifampin to classroom contacts, according to a multiclinic study in JAMA.

Study of a cohort of children in Seattle, Atlanta and the State of Oklahoma suggests that the risk of secondary disease (contraction of haemophilus by other children after classroom identification of a primary case) is strongly age related, with virtually all of the secondary cases occurring in children younger than 23 months.

David W. Fleming, MD, of the Centers for Disease Control in Atlanta, and colleagues point out that children older than 24 months can be vaccinated against haemophilus, but that the vaccine is not effective with children younger than 24 months. "These children may be at substantial risk for secondary Hib disease," they say.

The children are at even greater risk if they attend daycare more than 25 hours per week, study results suggest. Thus, a strategy other than vaccination is needed to prevent spread of disease.

"Our study provides evidence that, in practice, administration of rifampin to the high-risk, otherwise-unprotected day-care attendees aged 0 to 23 months significantly diminishes their risk of secondary day-care-associated Hib disease," the researchers assert.

A new strategy for disease control has become imperative because of the large numbers of youngsters attending day-care centers. Each year there are an estimated 12,000 cases of Hib-caused bacterial meningitis in the U.S., the researchers point out. "Nonmeningitic invasive Hib diseases account for a similar number of illnesses," they add.

"Although spread of Hib disease from one child to another was once thought to be rare, a number of recent

studies have demonstrated that the risk of secondary disease among household contacts is substantially elevated." Other studies had suggested that rifampin might prevent secondary cases, the researchers say. Their study confirms that suggestion, they conclude.

JAMA July 26, 1985

COMMUNITY ESTABLISHES DEFINITIONS FOR DO NOT RESUSCITATE ORDERS

An innovative policy that allows paramedics and emergency physicians to honor orders from nursing home medical records to not perform resuscitation is described in JAMA.

"The policy intends to partially address the unnecessary loss of patient autonomy that occurs when emergency care is administered according to routine orders," explain Steven H. Miles, H. Miles, MD, and Timothy J. Crimmins, MD, of the VA Medical Center and Hennepin County Medical Center respectively. Both centers are located in Minneapolis.

They explain that emergency care standing orders may conflict with the wishes of nursing-home residents and their families, when it is clear that use of emergency life support is inappropriate. The patient or family may ask that resuscitation be withheld, the family-care physician may endorse the request, the hospital and nursing home may accept it, but traditionally when the emergency team arrives, it follows its own orders to intervene dramatically to prolong life.

"This issue is of special concern when acutely ill nursing home residents are transferred from one health provider to another," the authors say. "The patient's personal physician is rarely able to supervise this phase of emergency care, and emergency personnel are usually unfamiliar with the patient's medical background and treatment plan."

The new policy defines directives to limit emergency care, gives procedures for the identification of valid directives, and endorses policies to encourage good decision-making practices in the formulation of these orders, they said. Specifically spelled out are instructions for do not resuscitate and do not intubate orders.

The authors say; that, to a large degree, this kind of policy properly returns emergency treatment decision-making to the nursing home residents and their personal physicians, who are acting on their behalf and with their consent. They add that response from public and professionals alike has been positive.

Commenting editorially, Bruce E. Haynes, MD, and James T. Niemann, MD, of Harbor/UCLA Medical Center in Torrance, Calif., say, "We view this policy as one long needed in prehospital care; it will allow physicians to assure that their patient's suffering is relieved when possible, yet rightfully let patients determine the extent of their medical care. It puts decision making where it belongs— in the hands of patients and their physicians."

JAMA July 26, 1985

WEIGHT LOSS KEY FACTOR IN BLOOD PRESSURE CONTROL

The most effective treatment for hypertension is weight loss, according to researchers writing in the July Archives of Internal Medicine. Working with information gained from the Multiple Risk Factor Intervention Trial, Richard H. Grimm, Jr., MD, PhD, of the University of Minnesota School of Public Health in Minneapolis, and colleagues report that men with elevated risk factors for heart disease assigned to special intervention groups fared better than those assigned to usual care groups in controlling blood pressure. But they add that "weight loss was associated with blood pressure lowering in both study groups, regardless of treatment status." In the study, a weight loss of 10 lbs was associated with a drop in diastolic blood pressure of up to 16.5 mm Hg.

PHOTODYNAMIC THERAPY EFFECTIVE FOR PORT-WINE SKIN STAINS

A new argon laser treatment for port-wine skin stains and other vascular lesions is described in the July Archives of Otolaryngology. Gregory S. Keller, MD, of the Western Institute for Laser Treatment in Santa Barbara, Calif., and colleagues report use of argon-dye laser hematoporphyrin derivative photodynamic therapy to treat vascular lesions in with a series of patients. The derivative is a tumor—sensitizing agent that selectively destroys tumor substance when exposed to laser light.

REPORT IMPROVED RESULTS IN DIABETIC AMPUTATIONS

Limb amputation is a feared complication for more than 4.2 million diabetic patients in the United States, but a report from Harvard Medical School appearing in the July Archives of Surgery suggests that amputation results today are significantly improved from results of 20 years ago. Compared were 100 consecutive below-knee amputations by Jeffrey Fearon, MD, and colleagues, with results of a similar study 20 years ago. Researchers report that 83 percent of patients today were ambulatory at discharge, compared with 63 percent 20 years ago. Aggressive surgical control of infection and early treatment of healing problems accounted for the improvements, the researchers say.

TIME FOR NEW RULES ON HEART DISEASE PREVENTION

Recent studies dictate a new strategy for primary prevention of coronary heart disease, asserts Nemat O. Borhani, MD, in JAMA.

"Physicians now face an unusual opportunity to participate successfully in the practice of primary prevention," says the researcher from the University of California, Davis. "To do this, however, we must identify among our patients the target populations at high risk, such as children and first-degree relatives of patients with documented coronary heart disease, and quickly detect and rigorously modify their risk most amenable to intervention, under medical supervision."

Borhani's article, one of a series sponsored by the American Heart Association, reviews some of the major clinical trials on multiple risk factors associated with heart disease. Results of those studies often have been confusing and misleading, he suggests. The Oslo Heart Study, for example, lends support to the strategy of controlling blood cholesterol and stopping cigarrette smoking.

"Direct extrapolation of the Oslo Trial experience to the general population, however, is not justified," he says. Like other trials, including the World Health Organization and Multiple Risk Factor Intervention Trial (MRFIT), results were not wholly convincing. Only minor differences between those who modified risk factors, including smoking, diet, exercise and weight, and those who did not were note in the studies. In the WHO study, risk modification resulted in a 7.4 percent reduction in fatal heart attacks; in MRFIT, a 7.1 percent reductions was noted.

By contrast, clinical trials involving individuals at elevated risk for heart disease demonstrated that medical intervention could produce dramatic results. The Lipid Reseach Clinics-Coronary Primary Prevention Trial (LRC-CPPT) showed that lowering blood cholesterol in a group of hypercholesterolemic patients resulted in a 19 percent reduction in coronary heart disease.

Similarly, the Hypertension Detection and Follow-up Program Cooperative Group (HDFP) showed a dramatic drop in coronary heart disease among individuals with elevated blood pressure when medical intervention was applied. A 26 percent reduction in disease was noted in the treated group in the trial.

Comments Borhani, "The results of all observational studies and clinical trials in aggregate seem to suggest that the most prudent policy of intervention would recognize the multifactorial nature of coronary heart disease and focus our primary prevention efforts on the top few percent of persons at really high risk by applying the proven method of a medical model of intervention. Results of the Oslo Heart Study, the LRC-CPPT, and the HDFP all seem to support such a strategy."

JAMA July 12, 1985

Medicolegal Decisions



HOSPITAL WINS ANTITRUST SUIT BY RADIOLOGIST

A county hospital was entitled to summary judgment in an antitrust action against it by a radiologist, a federal trial court in Georgia ruled.

The radiologist previously had an exclusive contract with the hospital. The hospital then entered into a new contract with another radiology group. The radiologist currently had privileges to perform second readings of radiological procedures at the hospital when requested by hospital patients. He also had family medicine privileges at the hospital. He filed an antitrust action against the hospital claiming that its exclusive contract with the radiology group was an illegal typing agreement.

Granting the hospital's motion for a summary judgment, the court said that the exclusive contract did not violate federal antitrust law. Patients could choose from among six radiologist at the radiology group, whereas formerly they had the choice of only the radiologist. There was no adverse effect of the exclusive contract on competition among radiologists. Nearby there were at least two other hospitals offering hospital and radiological services. One of those hospitals had an open-staff policy with regard to radiologists.

Concluding that there was no adverse effects on competition, the federal trial court granted the motion for summary judgment.--Mays v. Hospital Authority of Henry County, 596 F.Supp. 120 (D.C., Ga., Aug. 30, 1984).

TEXAS ALLOWS WRONGFUL BIRTH SUITS, BUT NOT WRONGFUL LIFE SUITS

A wrongful birth claim by the parents of a child born with Duchenne muscular dystrophy was not barred by the statute of limitations, but Texas law did not recognize the child's action for wrongful life, the Texas Supreme Court ruled.

The parents and their son filed suit against a physician and a university medical center. They alleged that the

physician negligently advised them that the mother was not a genetic carrier of Duchenne muscular dystrophy and was no more likely than any other woman to have a child afflicted by that disease. The parents claimed that had they known of this risk that the child would be born with the disease, they would have terminated the pregnancy. They also argued that the university negligently conducted or reported certain tests, causing the physician to misinform them.

A trial court granted summary judgment in favor of the physician and the university on the grounds that the statute of limitations barred the wrongful birth claim and that no cause of action for wrongful life existed in Texas. The court noted that the child had been diagnosed as having Duchenne muscular dystrophy at the age of three years and three months. The parents' claim for damages for wrongful birth was barred because it was not brought within two years of the last examination of their child by the physician, the trial court said. An appellate court affirmed the trial court's decision.

On appeal, the Texas Supreme Court affirmed the holding that no cause of action for wrongful life existed in Texas. To recognize such a cause of action would require the court to weigh the relative benefits of the child's impaired life as opposed to no life at all. If the physician and hospital had not been negligent, the parents would have known of the risk that their son would have Duchenne muscular dystrophy and would have aborted the pregnancy. The court said it was rationally impossible to decide whether the child had been damaged by being born.

The two-year statute of limitations, which began running on the date of the child's birth, violated the Texas constitutional provision guaranteeing a remedy by due course of law. The court said that the legislature had no power to make a remedy by due course of law contingent on an impossible condition. The child's condition was not diagnosed until more than a year after the two-year statute of limitations had expired, the court said. The court said that the statute was unconstitutional to the extent that it cut off an injured person's right to sue before the person had a reasonable opportunity to discover the wrong and bring suit. The court concluded that the parents' cause of action for wrongful birth to recover the expenses reasonably necessary for the care and treatment of their child's impairments was not barret by the two-year statute of limitations.

The claim for damages for wrongful birth was remanded for trial.--Nelson v. Krusen, 678 S.W. 2d 918 (Tex.Sup.CT., Oct. 17,1984; rehearing denied, Nov. 21, 1984)

MOTHER OF STILLBORN INFANT CAN SUE FOR WRONGFUL DEATH

A fatal prenatal injury to a viable fetus was actionable under the wrongful death and survival statutes, the highest court of the District of Columbia ruled.

A mother sought recovery against a physician and a hospital for allegedly negligent treatment, resulting in the stillbirth of a fetus in approximately the 33rd week of gestation. The hospital moved to dismiss on the grounds that no cause of action existed under either statute because a fetus was not a "person" under law. The trial court denied the motion, holding that a viable fetus was a "person" within the context of the statutes in question.

On appeal, the court said that a cause of action for wrongful death arises only if the deceased person could have sued if he or she had not died. A cause of action for injuries survives the person's death only if the cause of action accrued before death. In the present case, the question was whether the deceased fetus could have brought a common law action for prenatal injury if he had not died and whether the action accrued prior to his death.

The court pointed out that every jurisdiction in the United States had recognized a cause of action for prenatal injury to a viable infant later born alive. The court adopted the rationale in a prior, landmark, decision, where a judge based his decision on the established medical fact that a fetus was a person separate from its mother. A viable fetus was recognized as an independent person with the right to be free of prenatal injury. The court said that, assuming the allegations in the present case to be true, a negligence action for prenatal injury accrued to the fetus at the time of injury and, had he survived, he could have maintained an action for the injuries.

The survival act, the court said, recognizes that liability to a victim should not be extinguished by death. The action arises not from the death but from the injury itself. The act does not create a new cause of action for beneficiaries but preserves the cause of action that the deceased party would have had if he or she had not died. The court said that in both statutes, it makes no difference in liability whether the fetus dies of the injuries just before or just after birth. The court affirmed the trial court's order denying dismissal and sent the case back for further proceedings.—Greater Southeast Community Hospital v. Williams, 482 A. 2d 394 (D.C.Ct. of App., Oct. 9, 1984)

U.S. NOT LIABLE FOR STERILITY AFTER APPENDICITIS

The U.S. was not liable for a patient's sterility due to an abscess that formed after a ruptured appendix, a federal trial court in Alabama ruled.

On October 9, 1971, the young patient was taken to an emergency room by her mother because of abdominal pains, nausea, and vomiting. A physician diagnosed viral

gastroenteritis. Her condition did not improve, and the patient visited the hospital clinic the next week. From then until October 23, the patient was examined by various physicians and had various tests. The diagnoses considered included appendicitis, pyelonephritis, and gastroenteritis.

On October 23, an exploratory laparotomy revealed a ruptured appendix. The ovaries could not be seen because of an abscess. The appendix was not removed because of inflammation and the possibility of life-endangering bowel damage.

In March 1972, the appendix was removed. The surgeon found that the fallopian tubes were markedly scarred and inflamed and appeared to be occluded. He later testified that he had told the patient's mother that the patient might not be able to have children. She and her daughter denied that the conversation occurred.

The patient allegedly did not learn that her fallopian tubes were occluded until after her marriage, when a fertility expert examined her. In 1980, a second expert concluded that she was a poor candidate for reconstructive surgery. He said that the adhesions and scarring probably resulted from the pelvic abscess secondary to her ruptured appendix. The patient claimed that this was her first knowledge that the 1971 incidents caused her sterility.

The patient brought a malpraction action againt the U.S. under the Federal Tort Claims Act. The hospital denied that its employees were negligent and alleged that the suit was barred by the two-year statute of limitations.

After considering the evidence at trial, the court concluded that no one informed the patient or her mother of the injuries to her fallopian tubes in a way that was meaningful to either of them. When the patient visited one of the treating physicians several years after the surgery, he informed her that she had nothing to worry about. The court concluded that failure of the physicians to fully disclose the problem of sterility tolled the statute until 1980.

The patient contended that the physicians would have diagnosed appendicitis if they had performed a pelvic or rectal examination or taken a complete blood count. An appendectomy could have been performed before the pelvic abscess formed. The court agreed that the prevailing standards of care mandated such examination but was not persuaded that the physicians would have diagnosed acute appendicitis to the exclusion of other problems with sufficient certainty to require an immediate laparotomy. The court concluded that the delay, even if negligent, did not cause the patient's injuries. The court found that the patient could not recover.—Wilson v. U.S., 594 F.Supp. 843 (D.C., Ala., June 20, 1984)

HOSPITAL NOT LIABLE FOR DELAY IN TREATING PATIENT

As hospital was not liable for the alleged negligence of a private physician who had staff privileges at the hospital, a Florida appellate court ruled.

A young patient suffering from sickle-cell anemia was

taken to the emergency room by her sister. Upon her arrival, her private physician's medical group was contacted and various delays and uncertainties were encountered before her physician decided to admit her to the hospital. That delay allegedly contributed to the patient's death about four hours later. Her estate filed suit against the hospital claiming that it was liable for the acts of the physician. A trial court directed a verdict in favor of the hospital, and the estate appealed.

Affirming the lower court's decision, the appellate court said that the patient's physician was a private physician who was neither an agent nor an employee of the hospital. The hospital was not liable for the alleged negligence of the physician, who was an independent contractor to whom it had merely granted staff privileges, the appellate court said.—Reed v. Good Samaritan Hospital Association, Inc., 453 So.2d 229 (Fla.Dist.CT. of App., Aug. 1, 1984)

\$100,000 AWARDED IN WRONGFUL DEATH SUIT

The government of the Virgin Island was liable for \$100,000 in a wrongful death action based on medical

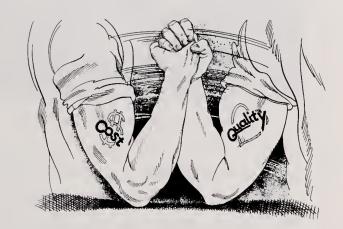
malpractice, a federal appellated court ruled.

A patient was visiting the island of St. Croix when she developed a severe headache. Her husband took her to a hospital that was owned and operated by the government of the Virgin Islands. There she was examined by a government-employed physician who prescribed some medication and instructed that she be taken home. She died several hours later of a cerebral hemorrhage. Her estate filed a wrongful death action against the government of the Virgin Islands, alleging that the physician's negligence was the cause of her death. A federal trial court awarded her \$100,000 in damages.

On appeal, the Virgin Islands argued that it was liable only for \$25,000 in damages. The Virgin Islands Tort Claims Act limited judgments against the government to \$25,000. The estate argued that the Virgin Islands Health Care Providers Malpractice Act expanded that liability to \$100,000.

Affirming the decision, the federal appellate court agreed that the malpractice act, which contained a mandatory malpractice insurance provision, expanded the government's waiver of immunity under the Tort Claims Act from \$25,000 to \$100,000 in medical malpractice actions.—Kock v. Government of the Virgin Islands, 744 F.2d 997 (C.A.3, Virgin Islands, Sept. 28, 1984)

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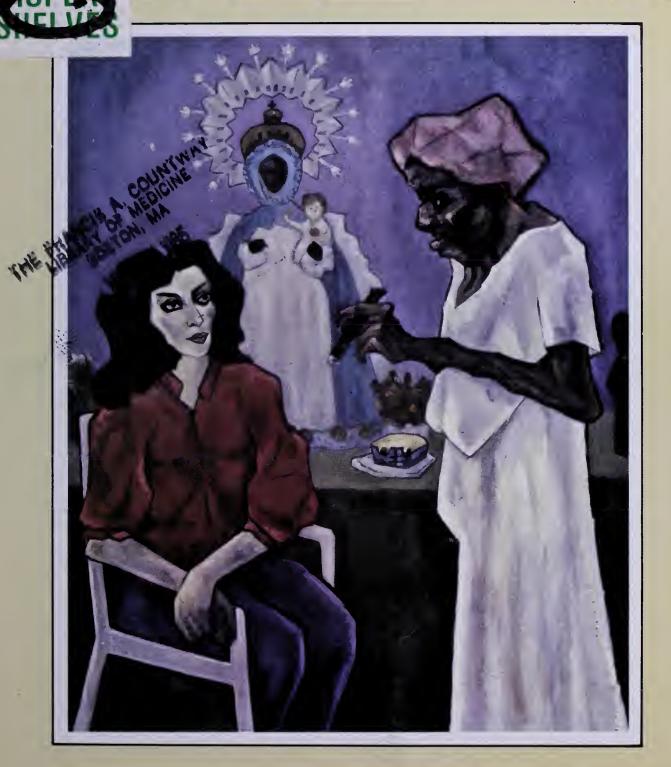
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VOL. 77/NUM. 10

OCTUBRE 1985



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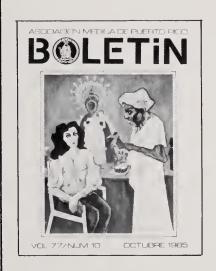


s conocido por nuestros lectores que por los últimos cuatro años la política de la Junta Editora ha sido la de publicar artículos de todas las ramas de la medicina. Se incluyen artículos que tienen que ver incluso con los aspectos sociales, económicos y éticos de la medicina. Otros Artículos Especiales han sido filosóficos, históricos o sencillamente informativos; siempre tratando de cumplir el objetivo de "diversificación" del contenido de la revista. Los Editoriales más bien son producto del análisis o de la opinión de algunos los miembros de la Junta Editora o de sus colaboradores sobre algún tema que se considere de relevancia para nuestra clase profesional. Muchos de ellos son controversiales y todos representan la opinión solamente del autor. El Boletín no toma lados en ninguno de los "issues" tratados en estos comentarios editoriales, ni estas opiniones representan el sentir de la Asociación Médica de Puerto Rico. Representan solamente el punto de vista del editorialista y van firmadas por el mismo. Como el resto de nuestro contenido estos editoriales son seleccionados por los miembros de la Junta en base a su interés general y originalidad.

Personalmente considero una parte esencial de la revista estos comentarios aunque no todos estemos de acuerdo con los mismos. Esto le imparte dinamismo, vitalidad y actualidad al Boletín. Creemos que con esta actitud le servimos mejor a la clase médica y que una revista como la nuestra debe dedicarle espacio a otras opiniones siempre que sean originales y de importancia. Confiamos que nuestros lectores estén de acuerdo.

Kinginii Suo

Rafael Villavicencio, MD, FACC Presidente Junta Editora Boletín Asociación Médica de Puerto Rico



NUESTRA PORTADA

Consultando. Oleo del artista puertorriqueño Jorge Rechany.

El autor nació en el Viejo San Juan en 1914 y a los 16 años comienza sus estudios de pintura con el profesor Alejandro Sánchez-Felipe. Luego de dos años estudia con el pintor Ramón Frade y en 1936 va a la National Academy of Design en Nueva York donde permanece hasta 1940. En la década del 50 viaja a México donde realiza estudios en la Escuela de Escultura y Pintura y en el Instituto Nacional de Bellas Artes. A principios de los años 60 se traslada a Europa y en viaje de estudios llega a Italia luego Holanda, Inglaterra, Francia y España. Luego de unos años en Puerto Rico el artista regresa a Nueva York en 1974 para continuar estudios en el Pratt Graphic Center de esa ciudad.

El artista ha expuesto sus obras en las principales galerías de arte de Puerto Rico, América y Europa, le han sido concedidos numerosos premios y distinciones tanto nacionales como internacionales y sus obras se encuentran diseminadas en colecciones públicas y privadas del hemisferio americano y europeo. Entre estas últimas cabe señalar que es Rechany el único artista puertorriqueño con una obra en el Vaticano. Es un óleo -La Magdalena- que se encuentra expuesto en el Museo Vaticano de Arte Sacro Moderno en la Ciudad del Vaticano, Roma.

Con relación a la obra de la portada, cuenta el autor que hace varios años mientras caminaba por el viejo San Juan sintió que le llamaban, y al girar se encontró con Doña Carmen Pagán, Santera de oficio y conocida desde su niñez. Después del saludo de rigor pasó a casa de ella donde le enseñó el "templo", un altar con figuras de varios santos y lugar solemne para Doña Carmen y sus creyentes. El misterio que permeaba este rincón junto con el misticismo que proyectaba la vieja Santera impresionó a Rechany de tal manera que su figura persistía en la mente del artista. Entonces decidió pintar a Doña Carmen en plena faena, atendiendo a las damas, muchas de ellas de la aristocracia capitalina que acudían a "consultar" y buscar remedio para los males del cuerpo y del alma através de las facultades de la Vieja Santera. Doña Carmen falleció hace un año y medio a la edad de 96 años.

La obra pertenece a la colección privada de Don Luis A. Ferré y su reproducción ha sido posible gracias a la gentileza del autor y de la Casa Amarilla, galería de arte en la Calle Navarro de Hato Rey.



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- 1. Reilly, EB et al. A comparison of the onset of bronchodilator activity of metaproterenol and isoproterenol aerosols. *Curr Ther Res* 1974; **16**: No. 8, 759-764. 2. Data on file at Boehringer Ingelheim Ltd.

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Warnings: Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of Alupent, brand of metaproterenol sulfate, as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases.

Paradoxical bronchoconstriction with repeated excessive administration has been reported with other sympathomimetic agents. Therefore, it is possible that this phenomenon could occur with Alupent, brand of metaproterenol sulfate

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Precautions: Because Alupent, brand of metaproterenol sulfate, is a sympathomimetic drug, it should be used with great caution in patients with hypertension, coronary artery disease, congestive heart failure, hyperthyroidism or diabetes, or when there is sensitivity to sympathomimetic amines

Information for Patients: Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent

Carcinogenesis: Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed

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Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Alupent, brand of metaproterenol sulfate, is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of Alupent Metered Dose Inhaler and Inhalant Solution in children below the age of 12 have not been established. The safety and efficacy of Alupent Tablets in children below the age of 6 have not been established.

Adverse Reactions: Adverse reactions are similar to those noted with other sympathomimetic agents

The most frequent adverse reactions to Alupent, brand of metaproterenol sulfate, are nervousness, tachycardia, tremor and nausea. Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste

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EDITORIAL

Board Certification

There are at least twenty three different medical specialties, each having and confering its own certification. To become Board Certified in any of the medical or surgical specialties a physician has to complete the required residency training and pass the board examination. Some boards require two examinations, the first written and the second an oral examination. In General Surgery the term Board Eligible is no longer accepted in spite of the candidate having obtained adequate training. After passing the written examination a surgeon is Board Qualified and after passing the second part he or she is Board Certified.

Physicians seek board certification on a voluntary basis, and in general there are several reasons why a physician may aspire and apply for board certification. Board certification might improve his or her referral sources or the opportunities for hospital privileges. Board certification implies that a physician has successfully completed some additional requirements beyond those required for a state license.

It is worrisome to know that only 20% of physicians in Puerto Rico have the specialty boards. In 1981, 53.2% of all United States physicians had obtained specialty certification and this figure has since increased at an annual rate of 7.2%, exceeding the annual growth rate for all practicing physicians.

The anticipated or probably the already present, surplus of physicians and therefore the increasing competition among them will provide an additional incentive to obtain board certification. Hospitals are being held responsible for faculty members actions, so it is anticipated that they will require better credentials including board certification. On the other hand, patients are better informed and they go directly to their specialist of choice and, at times, inquire about training and board certification.

Residency Review Committees in at least two recent decisions have mentioned as a serious concern the lack of board certification by faculty members. Residency Programs Directors should be aware of the increasing requirements being presently imposed.

All the above are good reasons for physicians to obtain board certification. However, the ultimate or fundamental reason should be pride, self-steem, recognition of our peers and even haughtiness. Nevertheless rationalization is used as an excuse for not taking the board examinations.

We should strive to improve the low rate of board certifications among our physicians. This could prove to be difficult in view of the limitations with the English language confronted by some of the potential candidates. Another difficulty encountered is the dual and disparate pathways to licensure in Puerto Rico. Most physicians in Puerto Rico have obtained adequate training in the primary medical or surgical specialties, while others have been permitted to practice after a locally accredited internship and a year of public service. This latter segment of our physicians population will most probably remain forever as general practitioners and do not qualify for board examination. This dual pathway will promote the undesirable two-tier medical service. Legislation is urgently needed to improve the present situation together with adequate incentives to recruit more and better young physicians for the indigent population.

In addition, we should be aware that recertification is already here and is being recommended and/or required by some of the Specialty Boards.

tunique vágy amitare M.D.

Enrique Vázquez-Quintana, M.D. Professor and Chairman Department of Surgery University of Puerto Rico School of Medicine



83ra. CONVENCION ANUAL Centro de Convenciones del Condado

Noviembre 6 a 11



Programa de Educación Médica Contínua Tentativo

MIERCOLES, 6 DE NOVIEMBRE

(Todo el día: Registro)

2:00 P.M. - Torneo de Golf - Dr. Ricardo Méndez Bryan

7:00 P.M. - Sesión Inaugural

JUEVES, 7 DE NOVIEMBRE

(Continúa el Registro de Participantes)

A.M.

J-2 — Medicina Industrial - Dr. C. Villafaña

J-2 — Sexualidad - Dr. A. López-Deynes

J-3 — Resuscitación Cardiopulmonar

J-4 — Hematología - Dr. Salomón Asmar

J-5 - Medicina Nuclear - Dr. Roberto Bordewick

P.M.

J-6 — Resuscitación Cardiopulmonar

J-7 — Medicina Física y Rehabilitación - Dr. Rafael Sein

J-8 — Urología - Dr. Antonio Puras

J-9 — Reumatología - Dr. Edwin Mejías, Dr. Salvador Vilá

J-10 - Computadoras - Sr. Jorge Calaf

VIERNES, 8 DE NOVIEMBRE A.M.

V-1 — Organización y Administración de la Oficina Médica
 Dr. Juan R. Colón Pagán

V-2 — Resuscitación Cardiopulmonar

V-3 — Medical Evaluation for Disability Claims Dr. T.G. Heibert

V-4 — Gastroenterología - Dra. Miriam Vicéns

V-5 — Oncología - Dr. Luis Báez-Díaz

P.M.

V-6 — Medical Evaluation for Disability Claims Dr. T.G. Heibert

V-7 — AIDS - Dra. María Santaella

V-8 — Resuscitación Cardiopulmonar

V-9 — Análisis Transaccional

Dr. Héctor Feliciano y Sra. Nereida Feliciano

V-10 — Cardiología - Dr. Félix Cortés

Viernes 12 M.

Conferencia Magistral Dr. Isaac González Martínez Dr. Franco Muggia - Profesor de Medicina y Director de Hematología/Oncología, New York University

SABADO, 9 DE NOVIEMBRE A.M.

S-1 — Temas Libres - Dr. Carlos Ramírez Ronda, Dr. Edgardo Hernández

S-2 — Resuscitación Cardiopulmonar

S-3 — Hipertensión - Dr. Rafael Ramírez-González

S-4 — Ginecología - Dr. Jose A. Roure/ Dr. Arsenio Comas

S-5 — Medicina de Adolescente - Dr. F. Ramos-Isern

P.M.

S-6 — Medicina Industrial - Dr. Carlos Villafaña

S-7 — Psiquiatría - Dr. William Galindez

S-8 — Temas Libres - Dr. Rafael Cox, Dr. Rafael Rodríguez-Servera

S-9 — Resuscitación Cardiopulmonar

S-10 — Sexualidad - Dr. Alejandro López Deynes

CAMARA DE DELEGADOS TODO EL DIA Actividad Social: Fiesta Tropical 7:30 P.M.

DOMINGO, 10 DE NOVIEMBRE A.M.

D-1 — Relaciones Públicas - Sra. Moraza, A.P.R.

D-2 — Resuscitación Cardiopulmonar

D-3 — Medical Evaluation Disability Claims Dr. T.G. Heibert

D-4 — Enfermedades Infecciosas - Dra. Julie Rodríguez

D-5 — Pediatría - Dr. Rafael Villavicencio

D-6 — Psiquiatría - Dr. Robert Stolberg

P.M

D-7 — Planificación Familiar y Fecundidad en Puerto Rico
 Dra. Rafaela Robles

D-8 — Medical Evaluation Disability Claims Dr. T.G. Heibert

D-9 — Dermatología - Dr. Jorge Sánchez

D-10 — Reembolso Medicare S.S.S. - Lic. Frank Fournier

D-11 — Resuscitación Cardiopulmonar

D-12 — Neumología - Dr. Ramón Figueroa Lebrón

DOMINGO 12:00 M.

Conferencia Magistral Dr. E. Fernández García

Dr. Sol Katz - Director Neumología, Universidad de Georgetown

LUNES, 11 DE NOVIEMBRE

9:00 - 11:30 A.M. — 2 sesiones de C.P.C.

Dr. Gustavo Ramírez de Arellano

Dr. Eliud López

11:30 A.M. hasta 1:00 P.M. —

Conferencia Magistral Dr. Ramón M. Suárez,

Dr. Elliot Rappaport

1:00 P.M. — TOMA DE POSESION

Before prescribing, see complete prescribing information in SK&F ${\rm CO.}$ literature or ${\it PDR.}$ The following Is a brief summary.

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in coch patient hyperate.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amilloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum Hypersensitivity to either component or other sulfonamide-

derived drugs.

Warnings: Do not use potassium supplements, dletary or other subnolaminate develops or dletary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of

reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus eythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity: Theoretically, a patient transferred from the single entities of Dyrenium (triametrene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphoterion. B or corticosteroids or corticotropin (ACTH)). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood st

Thiazides may add to or potentiate the action of other antihypertensive

Diuretics reduce renal clearance of lithium and increase the risk of lithium

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by aicohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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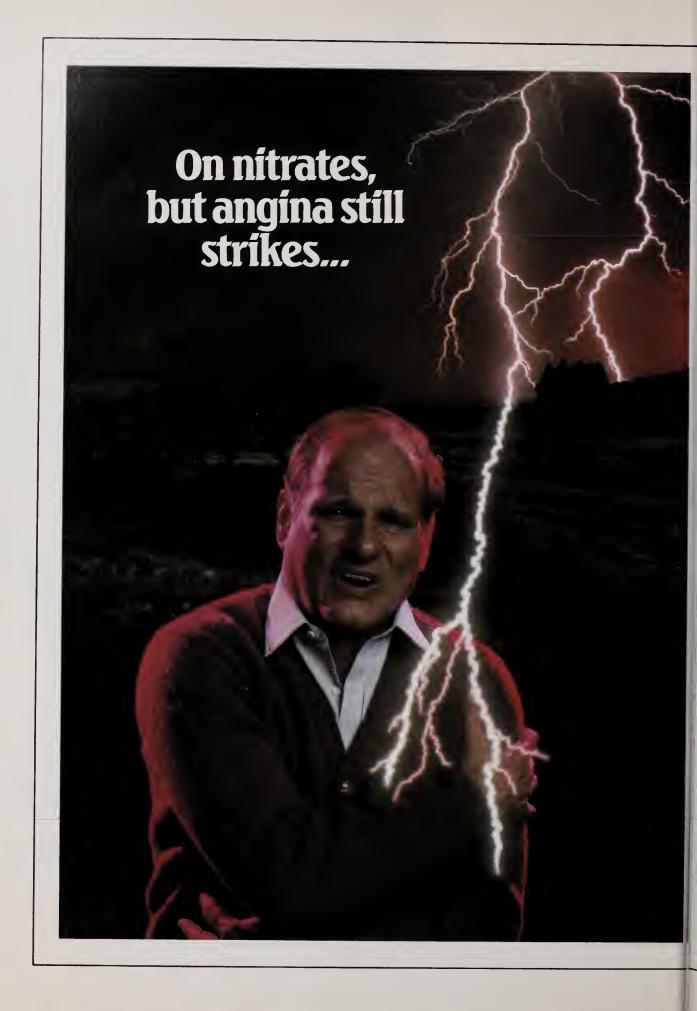
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left ventricular dysfunction,
hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome
(if no artificial pacemaker is present)
and second- or third-degree AV block.

So, the next time a nitrate is not enough, add Isoptin...for more comprehensive antianginal protection without side effects which may cramp an active life style.

ISOPTIN. Added antianginal protection without beta-blocker side effects.

ISOPTIN° (verapamil HCI/Knoll)

80 mg and 120 mg scored, film-coated tablets

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Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations may disappear even with continued treatment; however, four cases of hepatocellular injury by verapamil have been proven by rechallenge. Periodic monitoring of liver function is prudent during verapamil therapy. Patients with atrial flutter or fibrillation and an accessory AV pathway (e.g. W-P-W or L-G-L syndromes) may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion, which has been used safely and effectively after ISOPTIN. Because of verapamil's effect on AV conduction and the SA node, 1° AV block and transient bradycardia may occur. High grade block, however, has been infrequently observed. Marked 1° or progressive 2° or 3° AV block requires a dosage reduction or, rarely, discontinuation and institution of appropriate therapy depending upon the clinical situation. Patients with hypertrophic cardiomyopathy (IHSS) received verapamil in doses up to 720 mg/day. It must be appreciated that this group of patients had a serious disease with a high mortality rate and that most were refractory or intolerant to propranolol. A variety of serious adverse effects were seen in this group of patients including sinus bradycardia, 2° AV block, sinus arrest, pulmonary edema and/or severe hypotension. Most adverse effects responded well to dose reduction and only rarely was verapamil discontinued. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Chronic ISOPTIN treatment increase require discuss leads to 100 to 1 ment increases serum digoxin levels by 50% to 70% during the first week of ment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patients should be carefully monitored to avoid over- or under-digitalization. ISOPTIN may have an additive effect on lowering blood pressure in patients receiving oral antihypertensive agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Clinical experience with the concomitant use of ISOPTIN and short- and long-acting nitrates suggest beneficial interaction without undesirable drug interactions. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C*: There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR < 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%), elevations of liver enzymes have been reported (See Warnings.) The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: ecchymosis, bruising, gynecomastia, psychotic symptoms, confusion, paresthesia, insomnia, somnolence, equilibrium disorder, blurred vision, syncope, muscle cramp, shakiness, claudication, hair loss, macules, spotty menstruation. How Supplied: ISOPTIN (verapamil HCI) is supplied in round, scored, film-coated tablets containing either 80 mg or 120 mg of verapamil hydrochloride and embossed with "ISOPTIN 80" or "ISOPTIN 120" on one side and with "KNOLL" on the reverse side. Revised August, 1984.



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ESTUDIOS CLINICOS

Los Resultados de Trasplante Renal de Donante Vivo en Puerto Rico

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Resumen: El Programa de Trasplante de Puerto Rico comenzó en 1977, primero adscrito al Hospital de la Administración de Veteranos y más recientemente al Hospital Auxilio Mutuo. Este estudio informa nuestros resultados con 168 trasplantes llevados a cabo desde 1977. Tenemos datos completos de 103 trasplantes de donador vivo llevados a cabo en el Programa entre enero de 1977 y junio de 1984. La mayor parte de los pacientes eran varones, entre las edades de 21 a 50 años y de raza blanca. La evaluación de los donadores fue extremadamente estricta con criterios de exclusión muy rígidos. La técnica quirúrgica y el manejo post-trasplante has sido standard con la excepción de que en 1980 se alteró el régimen inmunosupresor para añadir suero antilinfocítico en la terapia de rechazo y a la vez disminuir drásticamente los requisitos de cortico-esteroides. Los resultados de sobrevida de paciente a 3 años plazo para toda la serie es de 92%, pero después de 1980, y quizás como reflejo de los cambios en inmunosupresión, aumentó la sobrevida a 98%. La sobrevida del injerto se ha mantenido estable entre 77 y 82% a 3 años plazo. La mayor parte de las muertes han sido secundarias a sepsis, casi todas relacionadas al manejo del rechazo. Todas las pérdidas de riñón fueron secundarias a rechazo. Informamos una tasa relativamente baja de complicaciones urológicas y técnicas. También informamos una alta prevalencia de hongos cutáneos y, sin embargo, una incidencia casi ausente de hongos sistémicos. Correlacionamos estos resultados con factores relevantes, con atención a detalles técnicos y médicos.

L a incidencia de enfermedad renal terminal en Puerto Rico ha cambiado de la observación inicial de 44 casos nuevos por millón por año, a los cálculos más recientes de 119.2 casos nuevos por millón por año. Indudablemente este cambio refleja los adelantos en diagnóstico, la mejora en comunicación, un programa

activo de diseminación de información a la comunidad, y el aumento en las facilidades para el cuido del paciente renal. Actualmente existen ocho centros de hemodiálisis de hospital, ocho unidades de diálisis satélite, ocho programas de diálisis peritoneal ambulatoria, y ocho de peritoneal contínua; un programa de trasplante renal (inicialmente en el Hospital de Veteranos y actualmente en el Hospital Auxilio Mutuo), un programa de entrenamiento en cirugía de trasplante, dos programas de entrenamiento en nefrología, un laboratorio de histocompatibilidad, un Consejo de Enfermedades Renales (#29), varias organizaciones de profesionales renales y de pacientes, y una Fundación Puertorriqueña del Riñón, servicios que están disponibles a una población de 3.2 millones de habitantes. El Programa de Trasplante de Puerto Rico comenzó en enero de 1977 ubicado en el Hospital de Veteranos de San Juan, Puerto Rico pero sirviendo predominantemente a pacientes de la comunidad, situación que eventualmente resultó en el traslado del Programa al Hospital Auxilio Mutuo.

La ausencia de una legislación que específicamente hablara de muerte cerebral hizo difícil el desarrollo de un programa de trasplante de cadáver por muchos años. En septiembre de 1983, la Ley de Donaciones Anatómicas del 1974 fue enmendada para incorporar una definición de muerte que incluyera muerte cerebral. Como consecuencia, por muchos años nuestro Programa de Trasplante se dirigió principalmente a trasplantar de donantes vivos. El presente estudio resume los resultados de 103 trasplantes de donante vivo que se llevaron a cabo en Puerto Rico de 1977 a 1984 en el Hospital de Veteranos. De los 43 trasplantes llevados a cabo en el Hospital Auxilio Mutuo 29 has sido de donador vivo, pero, por lo reciente de la cirugía se nos hace difícil incorporarlos en la casuística total, y los discutiremos en secciones y comentarios aparte.

Materiales y Métodos

Población de pacientes. El total de trasplantes hechos de enero 1977 a septiembre de 1985 es de 178, con un total

De los Programas de Trasplante, Hospital de Veteranos (1977-1984) y Hospital Auxilio Mutuo (1983-1985)

de 133 trasplantes de donante vivo, 41 trasplantes de cadáver, y 4 autotrasplantes. Hemos analizado en detalle el historial de trasplante de 103 recipientes de órganos de donante vivo que se hicieran de 1977 a 1984. Examinamos la historia desde el punto de vista de sobrevida de paciente y de riñón, rebuscando además complicaciones inmunológicas, técnicas, y no técnicas.

En la casuística seleccionada encontramos 66 varones y 37 hembras. La edad fluctuó de los 5 a los 61 años. Hubo 6 niños y 13 adolescentes. Treinta y tres pacientes se consideraron indigentes, 62 clase media, y 8 clase media alta.² En nuestra distribución por raza usamos color y rasgos faciales, dada la dificultad causada por la mezcla de elementos negro africano y blanco europeo que existen en nuestra población.³ Consideramos 19 como probablemente negros, 63 como probablemente blancos, y 21 como mezclados.

Los criterios de exclusión para trasplante incluyeron la presencia de cáncer, enfermedad hepática, alcoholismo, enfermedad pulmonar severa, y una prueba cruzada ("cross-match") positiva. La etiología de la enfermedad renal se enumera en la Tabla I. La gran mayoría de los pacientes vinieron al Programa con diagnóstico de glomerulonefritis crónica, diagnóstico usualmente de índole clínica.

Tabla I

Glomerulonefritis crónica	53
Enfermedad renal terminal (no especificada)	18
Pielonefritis crónica o nefritis intersticial	8
Estructural y obstructiva	8
Hipertensión	7
Nefritis hereditaria	2
Nefropatía diabética	2
Púrpura de Schoenlein-Henoch	2
Nefropatía por IgA	1
Lupus	1

Donantes. Hicimos todo el esfuerzo posible para evaluar el mayor número de donadores posible con la esperanza de encontrar familiares idénticos en HLA. La Tabla 2 demuestra la distribución de donantes por parentesco. Nuestro Programa siempre ha sido extremadamente rígido con la evaluación y selección de donantes vivos. La intención es proteger al donante ante todo. El donante tiene que estar "100% saludable". Con estos criterios rechazamos 33% de los posibles donantes, las razones incluyendo obesidad, hipertensión leve, infección urinaria, litiasis renal, enfermedades metabólicas y úlcera péptica, entre otras.

Tabla II

Donantes		
Madre	15	
Padre	13	
Hermano	33	
Hermana	33	
Hijo	4	
Hija	2	
Sobrino	2	
Primo	1	

Histocompatibilidad. Tipificamos para HLA-A,B, y C en el Laboratorio de Histocompatibilidad de Puerto Rico el cual incialmente estuvo en el Hospital de Veteranos y eventualmente en el Departamento de Patología de la Escuela de Medicina de la Universidad de Puerto Rico. Utilizamos las técnicas de microtoxicidad de NIH y el cultivo mixto de linfocitos. Intentamos usar por lo menos dos antígenos en común y el haplotipo cuando lo podíamos obtener. Basándonos en un estudio previo⁴ el índice de estimulación de linfocitos nos sirvió para identificar la reactividad celular. Un índice alto (mayor de 3) lo consideramos como indicación para dar transfusiones de sangre de su donador específico. Otras pruebas que medían la inmunidad celular tales como la transformación inducida por fitohemaglutinina y la prueba de piel a antígenos comunes, las eliminamos del protocolo por su falta de correlación con morbilidad y mortalidad⁵ y por no guardar relación con los resultados finales de trasplantes.⁴ Con la introducción de la ciclosporina en nuestro Programa seguimos utilizando la similitud histogénica cuando es posible. No obstante, si el único donante que existe no tiene un haplotipo o dos antígenos en común procedemos a hacerlo con cubierta de ciclosporina y le explicamos que la probabilidad de éxito disminuirá un poco.

Esplenectomía. Hemos practicado intermitentemente la esplenectomía pre-trasplante en nuestro Programa. La utilizamos de manera rutinaria entre 1977 y 1979. En el 1979 descontinuamos la operación y comenzamos un estudio piloto sin esplenectomía, ya que la evidencia de sepsis post-esplenectomía nos obligaba a un escrutinio crítico de este procedimiento. No obstante, encontramos un aumento significativo en la severidad del rechazo y esto forzó el reinstituir la práctica como parte de protocolo de inmunosupresión. Más recientemente, sin embargo, hemos vuelto a eliminar la práctica de la esplenectomía de nuestro Programa al adoptar la inmunosupresión con ciclosporina en todos nuestros casos.

Técnica quirúrgica. La nefrectomía del donante se lleva a cabo mediante una incisión en el flanco. Se hidrata al donante lo mejor posible⁷ y utilizamos manitol y heparina antes de la oclusión vascular. La manipulación durante la disección es mínima y se procura remover el riñón tan solo cuando está con una diuresis máxima. Después de perfundirlo, se trasplanta a la fosa iliaca derecha del recipiente usando técnica vascular standard. La vena siempre se anastomosa término-lateral a la ilíaca externa o común, y la arteria se anastomosa términolateral a la externa o a la común, o término-terminal a la interna.8 En niños las anastomosis las hacemos a la vena cava inferior y a la aorta. De 1977 a 1981 usamos la técnica de ureteroneocistostomía de Politano-Leadbetter. En los últimos cuatro años hemos usado una modificación de la operación Lich-Gregoir; la referencia 8 describe la técnica en detalle. En niños con anormalidades en la vejiga hemos usado conductos iliales, conductos ileocecales, o el trasplante a una ureteroctomía previa madura.9 Apróximadamente en la mitad de los casos dejamos drenaje cerrado lateral al riñón, los cuales removemos en 48 horas. Durante la cirugía irrigamos copiosa y frecuentemente la cavidad expuesta con solución de antibióticos.

Manejo post-trasplante. Todos los recipientes se hidratan a un máximo y la rutina es una diuresis posttrasplante masiva. El catéter vesical suele removerse el segundo día, a menos que la diuresis sea tan exagerada que nos preocupe la integridad de la línea de sutura.

Podemos dividir nuestra inmunosupresión en tres períodos. El primer período de 1977 a 1980 utilizamos prednisona, azatioprina, y suero antilinfocítico de Minnesota como inmunosupresión profiláctica, y para rechazo utilizamos metilprednisolona y aumento de la prednisona oral. 10 De 1980 a 1984 disminuímos dramáticamente la cantidad de prednisona que profilácticamente le dábamos a los pacientes. Disminuímos rápidamente la prednisona después del trasplante, dando al paciente de alta dos o tres semanas después del trasplante en una dósis mínima de 20mg al día. Eventualmente, al año, en vez de recibir 0.3mg/kg estaban ya entre 0.15 y 0.20mg/kg por día. El otro cambio fue la introducción del suero antilinfocítico como terapia para el rechazo en vez de aumentar la prednisona o confiar exclusivamente en la metilprednisolona intravenosa. El tercer período comenzó en el 1984 cuando hemos confiado casi exclusivamente en la ciclosporina como terapia inmunosupresora. En este último período damos dosis intermedias de ciclosporina, dosis bajas de prednisona, y más recientemente dosis mínimas de azatioprina, en un intento de reducir aún más la ciclosporina y su toxicidad.

La evaluación post-trasplante incluye perfiles hepático, hematológico y renal, urinálisis, y medida de presión arterial y peso en intérvalos frecuentes: 3 veces por semana por un mes, 2 veces por semana por dos meses y semanalmente hasta los 6 meses. Le damos mucho valor a un urinálisis cuidadoso hecho en un especimen fresco, ya que la leucocituria persistente aparenta tener valor pronóstico. De rutina se hace sonografía y estudios funcionales y anatómicos con radioisótopos después del trasplante y en casos de disfunción renal. Con estos estudios raras veces utilizamos el pielograma o el arteriograma en la evaluación de disfunción post-trasplante. Todo paciente con fiebre se ingresa al hospital. Toda infección, en particular infecciones pulmonares, se maneja con agresividad extrema. La serología viral se hace de rutina.

Resultados

Sobrevida. La Tabla III presenta la sobrevida del paciente y del riñón la cual hemos calculado utilizando el método actuarial (Life-Table Analysis). La sobrevida del paciente a tres años plazo para el total de 7 años y medio es 91.6%. Sin embargo, si analizamos tan solo los pacien-

Tabla III

Sobrevida de Pacientes e Injertos					
	1 Mes	6 Meses	1 Año	2 Años	3 Años
Sobrevida Paciente					
1977-1984	100	96	94	93	91.6
1980-84 solamente	100	98	98	98	98
Sobrevida injerto					
1977-1984	97.1	91	89	84.6	81.7
1980-84 solamente	96	94	89.9	83	77

tes trasplantados de 1980 a 1984, como un índice de los cambios en la inmunosupresión profiláctica y en el manejo del rechazo, la sobrevida de pacientes a 3 años plazo aumentó a 98%. Este aumento en sobrevida alteró muy poco los resultado de sobrevida de injertos a 3 años plazo.

La mayor parte de las muertes las relacionamos al manejo del rechazo: ocurrieron bien sea durante el manejo del rechazo o inmediatamente después. Ochenta porciento de las muertes se debieron a sepsis bacteriana (Tabla IV), aunque hubo un caso de Strongyloides stercoralis diseminado en uno de los recipientes, 13 no asociado a rechazo. Hacemos hincapié que después de instituir el uso de suero antilinfocítico como terapia de rechazo y de bajar la dosis de prednisona inmunoprofiláctica la mortalidad relacionada a rechazo disminuyó a 0. Tres casos de pérdida renal tardía se debieron a recurencia de la enfermedad. Todas las otras pérdidas se debieron a rechazo agudo (9 casos), rechazo acelerado, rechazo crónico (6 casos), o rechazo crónico con rechazo agudo sobreimpuesto (4 casos). En general los riñones removidos en los primeros 6 meses tenían rechazo agudo y aquellos después de los 6 meses contenían rechazo crónico con o sin rechazo agudo sobreimpuesto (p < .01, "Chi Square").

No pudimos descubrir ningún índice selectivo de mortalidad, y en especial, no se relacionó ni el status socioeconómico ni la raza. Sin embargo, la raza aparentó tener un impacto independiente en la pérdida renal ya que 35% de los recipientes negros o mixtos perdieron el riñón vs 13% en blanco (Chi Square = 7.24; p = 0.007). Este hallazgo no se podía explicar por status socioeconómico, hogar, incidencia más alta de infección o hipertensión.

Tabla IV

Muertes	
Sepsis	
Aneurisma micótico aórtico (Salmonella)	1
Endocarditis bacteriana aguda (S. aureus)	1
Sepsis fulminante (E. coli)	1
Pulmonía necrotizante (K. pneumonia)	2
Pulmonía (P. carinii)	1
Pulmonía y fallo respiratorio	1
S. stercoralis diseminado	1
Embolia pulmonar	1
Pancreatitis, obesidad, fracturas	I

Infecciones. La Tabla 5 describe nuestras complicaciones infecciosas. Comunmente encontramos infecciones urinarias y prostatitis, casi siempre sintomáticas y benignas, respondiendo rápidamente a antibioterapia. Todavía vemos periódicamente tuberculosis pero la mayor parte de nuestros casos respondieron rápidamente a terapia antituberculosa. Fueron también frecuentes las infecciones respiratorias de tracto superior, la pulmonía y los virus, pero éstos eran relativamente leves y respondían rápidamente a terapia antimicrobiana.

Sin embargo, encontramos con gran frecuencia la micosis cutánea. En un estudio (para publicarse) encontramos que 60% de nuestros pacientes tenían evidencia de epidermofitosis, 10% de los cuales eran

severamente sintomáticos. Esto no tuvo relación con raza, edad, o con status socioeconómico, pero encontramos correlación entre la severidad y la dosis de azatioprina y prednisona (p<0.5). A la inversa, y para nuestra gran sorpresa, hemos encontrado que los hongos sistémicos están totalmente ausentes de nuestra población trasplantada, con excepción de un caso con meningitis secundaria a criptococco en un paciente que había viajado extensamente por Europa. (Este paciente se trató con éxito con anfotericina-B y fluocitosina).

Las infecciones "raras" no son tan raras en nuestro Programa (Tabla 5). De interés particular informamos una pulmonía por *M. kansasii*, ¹⁴ y un paciente con cromoblastomicosis subcutánea, ¹⁵ ambas tratadas exitosamente. La apendicitis es muy rara en el paciente trasplantado pero a fines de 1984 tuvimos dos pacientes casi simultáneamente con apendicitis perforada y abscesos intraabdominales. Ambos pacientes sobrevivieron y están bien después de terapia quirúrgica agresiva.

Tabla V

Infecciones		
Común	Rara	
Infección urinaria	Pulmonía M. kansasii	
Prostatitis	Sepsis L. monocitógenes	
Tuberculosis	Sepsis Salmonella sp	
Pneumonia	Pulmonia P. carinii	
Infección respiratoria	Pulmonía M. morgagni	
Virus	Pulmonía Estafilococcica necrotizante	
Hongos de piel	Sepsis S. stercoralis	
Parásitos intestinales	Cromoblastomicosis	
	Encefalitis Herpes	
	Hepatitis Toxoplasma	
	H. zoster diseminado	
	Apendicitis perforada con absceso	
	Aneurisma micótico aórtico	

Complicaciones técnicas. Informamos una baja frecuencia de complicaciones urológicas, la más dramática siendo una paciente con necrosis tubular aguda tan severa que desarrolló necrosis total del uréter y la pelvis renal (Tabla VI). Todas las complicaciones, incluyendo la necrosis mencionada, se resolvieron con intervención quirúrgica pronta. Los linfoceles los manejamos con aspiraciones repetidas pero si recurren llevamos a cabo una marsupialización interna la cual suele ser curativa. No hemos visto trombosis arterial ni venosa. No hemos tenido infecciones profundas y no hemos perdido paciente o riñón debido a complicaciones técnicas.

Otras complicaciones (Tabla VII). Hemos visto relativamente poco carcinoma a pesar de estar en un país tropical. Un hombre de 58 años ha desarrollado un carcinoma espinocelular en el dorso de la mano, leucoplaquia en el labio, y una lesión pulmonar.

Trasplantes más recientes. De septiembre de 1983 a septiembre de 1985 se llevaron a cabo 43 trasplantes en el nuevo Programa de Trasplante en el Hospital Auxilio Mutuo, 29 de los cuales eran de vivos y 14 de cadáver. Siete eran adolescentes y 1 era un niño de 5 años, el más pequeño hecho en el país, con un peso de 14 kilos. Un

Tabla VI

Complicaciones Técnicas	
Complicaciones urológicas	
Estenosis ureteral temprana	3.9%
Estenosis ureteral tardía	1.9%
Nefrolitiasis	1.9%
Extravasación	0.9%
Necrosis total ureteral	0.9%
Linfocele	6.7%
Insuficiencia renal aguda (diálisis temporera)	5.9%
Hemorragia	3.9%
Infección	
Superficial	2.9%
Profunda	0%
Anastomosis	0%
Estenosis temprana de la arteria renal	0.9%
Hernia	0%
Complicaciones venosas	0%
Pérdida por razones técnicas	0%
Muerte por complicaciones técnicas	0%

Tabla VII

Complicaciones Miscelaneas			
Hipertensión	31%		
Diabetes inducida por esteroides	8.5%		
Necrosis aséptica de la cadera	4.9%		
	(3 casos bilaterales)		
Estenosis tardía de la arteria renal	3.9%		
Tromboflebitis profunda	2.9%		
Cataratas con daño visual severo	1.9%		
Cáncer			
Tumor linfoide pulmonar	0.9%		
Adenocarcinoma del recto	0.9%		
Carcinoma in situ de vulva	0.9%		
Carcinoma espinocelular de la piel	0.9%		
Displasia del cervix uteri	0.9%		

riñón de cadáver se perdió en sala de operaciones después de 40 horas de perfusión con daño severo por perfusión o quizás cambios agonales en el cadáver imposibles de predecir antes del trasplante. Se han perdido 2 riñones adicionales, uno por estrechez severa de la arteria renal y rechazo crónico severo, y el otro con un rechazo agudo severo. Cien porciento de los pacientes viven, 89% con un riñón trasplantado. Los números son muy pequeños y no permiten hacer un análisis como en el grupo anterior. De los 43 pacientes, los últimos 30 han recibido ciclosporina y prednisona como terapia inmunosupresora.

Discusión

El trasplante renal ya es rutinario en el manejo de la enfermedad renal permanente. Nuestra casuística se comporta más o menos como la que otros centros grandes de los Estados Unidos informan. No obstante, hay ciertos puntos sobresalientes que son peculiares a nuestra experiencia. La sobrevida de paciente mejoró significativamente al cambiar nuestro protocolo de inmunosupresión. El uso del suero antilinfocítico para rechazo junto con el uso conservador de la prednisona ha resultado en un aumento significativo e importante en la sobrevida de pacientes en comparación con la sobrevida

de Estados Unidos. ¹⁶ Estamos menejando el rechazo más temprano y más agresivamente con el suero antilinfocítico a la vez que evitamos la sobredosis de esteroides que tanto daño hacían en la práctica de los trasplantes.

No tenemos explicación para la incidencia tan baja de hongos sistémicos. En Puerto Rico se han reportado el *Histoplasma*, el *Sporotrix*, la *Candida*, y el *Aspergillus*, todos los cuales son organismos muy importantes en las complicaciones infecciosas en Estados Unidos y Europa. A la inversa, reportamos una incidencia alta de micosis cutánea, probablemente un reflejo de la humedad y la temperatura.

También hemos visto una incidencia baja de tumores cuando comparamos con el promedio nacional.¹⁷ De particular interés es la incidencia tan baja de tumores de piel, ya que Puerto Rico es un país tropical que tiene un índice ultravioleta alto. Diecinueve porciento de los pacientes trasplantados en Australia desarrollan cáncer de piel, ¹⁸ y en Suecia más o menos lo mismo. Sospechamos que esta incidencia tan baja puede ser reflejo del seguimiento tan corto de nuestros pacientes (Penn, I., comunicación personal) o de nuestra mezcla racial.

La incidencia de infecciones de herida es muy baja y puede ser resultado de la baja incidencia de complicaciones urológicas, del uso profiláctico de antibióticos durante e inmediatamente post-operatorio, y del uso de irrigación copiosa y contínua durante la cirugía.

Otro factor importante en los resultados de sobrevida lo es la agresividad con el paciente infectado la cual permite diagnosticar temprano las infecciones raras y comunes e instituir el tratamiento indicado con prontitud. En el caso de las infecciones pulmonares, consideramos prioridad la identificación del organismo de manera que hacemos uso liberal de la broncoscopía con biopsia para este diagnóstico.

Summary: The Puerto Rico Kidney Transplant Program was started in January 1977 first at the San Juan Veterans Administration Hospital and more recently at the Auxilio Mutuo Hospital. The present study reports our experience with 167 kidney transplants performed since January 1977. Of these, we have full information on 103 kidney transplants from living related donors performed between January 1977 and June 1984. The majority were male, between 21 and 50 years of age, and caucasians. Donor evaluations were performed under very rigid criteria. Surgical technique and post-transplant immunosuppression were standard except for 1980 when, we changed our immunosuppression protocol to include antilymphocyte globulin in the management of rejection and to diminish the use of steroids both prophylactically and therapeutically. The overall 3-year patient survival for the whole period is 92%, but after the changes performed in immunosuppressive protocol, it increased to 98%. Kidney survival has remained the same at a level of 77 to 81% 3-year graft survival. Most deaths were related to sepsis usually occurring during or immediately subsequent to treatment of rejection. All kidney losses were due to rejection with a relatively low incidence of urological and technical complications. Skin fungi were prevalent in our patients whereas systemic fungi were almost absent. Careful attention to

technical and medical factors may explain in part our results.

Agradecimiento

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Study of Delirium at the University District Hospital

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Given the high mortality rate among delirious patients it is very important to make an early diagnosis and treat the underlying cause(s) or etiology(ies).

The authors intend to perform a general study on delirium at the University District Hospital, to obtain general information about delirious patients such as sex, age, services in charge of the patients and the incidence of this syndrome at this setting.

The facilities of the Liason Consultation Division of the Department of Psychiatry at this hospital, and the computerized information in the medical records were used to elaborate this study.

Psychopathology

Delirium is a transient, reversible, organic mental disorder, of relatively acute onset, characterized by global impairement of cognitive functions and widespread disturbance of cerebral metabolism.¹ It is manifested by diffuse dysfunction of neural tissue including the cerebral hemispheres, the reticular activating system, and usually the autonomic nervous system.²

Delirium is characterized by concurrent disturbance of wakefulness and sensorium, cognition and psychomotor activity.^{1, 3}

The thought processes are defective, disorganized and fragmented. The acquisition, processing, retention and utilization of information are all impaired.¹, ⁴, ⁵ Reasoning, problem solving and abstration are reduced.

Perception is impaired and this can be easily detected clinically. Objects may be perceived as distorted. Illusions and hallucinations can be found. Both illusions and hallucinations are specially common when environmental factors make sensory discrimination difficult. Probably that is why they are worst at night.

Partial-temporal disorientation is demonstrable in delirium. The patient is always at least midly disoriented in time. In more severe cases, disorientation in place and even person is not uncommon.

There is impairment in registration, retention, and recall of memories and testing usually demonstrates defects in inmediate, recent and remote memories.²

Some alterations in the wakefulness and sensorium is a sine qua non for the diagnosis of delirium. It can be manifested by a change in alertness, vigilance and arousal (attentiveness) to self and environment. The alertness can be decreased or increased and the vigilance is always

reduced. It can be also manifested by a reduction in awareness; going from unawareness of simple details to stupor. There is a disordered sleep-wake cycle. Night sleep can be reduced, fragmented and the wakefulness will be increased. It is not uncommon for patients to become delirious at night and be lucid during daylight.

Disturbances of psychomotor activity is another of the major findings in the delirious patient. A delirious patient may be hypoactive or hyperactive or even both, with restlessness more evident during the night.

A variety of involuntary movements may be present in delirum but there are two specific abnormalities of motility that require special attention because actually they are considered pathonognomic of delirium. Those are bilateral asterixis and multifocal myoclonus. According to Wells only asterixis and multifocal myoclonus possess any degree of diagnostic specificity for delirium; other signs and symptoms are nonspecific.²

Outcome, Diagnosis and Causes of Delirium

Delirium appears acutely (hours to days) and clears up completely, in the majority of the cases, in less than a month. Some cases progress to dementia or another organic disorder.

Some studies report that mortality rate can be higher in the delirious patient.^{1, 5} Failure to diagnose delirium and to identify and treat its et logy may have lethal consequences.

For the purpose of this study we are going to use the criteria of the DSM III for the diagnosis of delirium specified on table I.⁶

TABLE I

Criteria for the Diagnosis of Delirium

- A. Clouding of consciousness (reduced clarity if awareness environment), with reduced capacity to shift, focus, and sustain attention to environmental stimuli.
- B. Al least two of the following:
 - (1) perceptual disturbances: misinterpretation, illusions, or hallucinations.
 - (2) speech that is at time incoherent,
 - (3) disturbance of sleep-wakefulness cycle with insomnia or daytime drowsiness.
 - (4) increase or decreased psychomotor activities.
- C. Disorientation and memory impairment (if testable).
- D. Clinical feature that developed over a short period of time (usually hours to days) and tend to fluctuate over the course of a day.
- E. Evidence, from the history, physical examination, or laboratory test, of a specific organic factor judged to be etiologically related to the disturbance.

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Delirium has an organic etiology. Almost any physical condition may give rise to delirium. It may result from a single or a combination of factors that cause widespread disturbance of cerebral metabolism.

The causes may be extracraneal or intracraneal, the former being more common than the primary cerebral one.¹, ², ⁵ No single cause has been identified as the most common one of delirium although in the elderly the use of drugs with anticholinergic properties probably constitute the single most common cause of delirium in this age group.⁵

Table II lists some of the common causes of delirium. There are several factors that may predispose to delirium. Increased susceptibility to delirium is common among: geriatric patients, patients with history of addiction to drugs,^{2, 5} patients with history of alcoholism,^{2, 5} persons with brain damage of any type^{2, 5} and patients with chronic disease; cardiac, hepatic, renal and pulmonary dysfunction. Also psychological stress, sleep and sensory deprivation, severe fatigue and prolonged inmovilization may facilitate the onset of delirium.^{3, 5}

In 5 to 20% of the cases the etiologic factors may not be identified.⁵

TABLE II

Common Organic Causes of Delirium

- Cardiovascular disorders such as: congestive heart failure, myocardial infarction, endocarditis, arrhythmias, others.
- 2. Cerebrovascular accidents
- 3. Drug intoxication and withdrawal.
- 4. Hormonal disorders such as: hyperthyroidism, hypothyroidism, hyperparathyroidism, hypoparathyroidism, Cushing's syndrome, Addison's disease, others.
- Infections such as: pneumonia, septicemia, meningitis, urinary tract infections.
- 6. Metabolic disorders such as: hypoxia, hypoglycemia.
- 7. Neoplasm: primary and metastatic.
- 8. Nutritional disorders such as: avitaminosis and hypervitaminosis.
- 9. Traumas such as: burns, surgery, fractures.
- 10. Fluid and electrolyte imbalance.

Neuropathophysiology

Several hypothesis had been proposed to explain the occurrence of delirium:

- 1. widespread disturbance of cerebral metabolism; evidence provided by changes in E.E.G. with slowing of dominant E.E.G. rhythm during delirium that shift to the opposite direction with agitated delirium.⁷
- 2. impairement of brain oxidative metabolism that results in reduce synthesis of neurotransmitters, specially acetylcholine.⁵, ⁸ Affecting both cortical and subcortical structures.
- imbalance between acetylcholine and noradrenaline, between central cholinergic and adrenergic mechanism. Affecting the medical ascending reticular activating system and the medial thalamic projections.

The neuropathologic changes, that are nonspecific and bilateral, include diffuse cerebral swelling of cortical and hippocampal neurons and disolution of Niss granules. 1, 2, 3, 9

Differential Diagnosis and Treatment

According to DSM III delirium has to be distinguished from other conditions such as schizophrenia, schizophreniform disorder, other psychotic disorders, dementia, factitious disorder with psychological symptoms and pseudodelirium.

Differential diagnosis is often complicated by the concurrence of delirium and dementia. In an already demented patient the features of delirium tend to be modified. Complex hallucination, dreamlike mentation, and confabulations are frequently lacking, and the patient exhibits mostly apathy interrupted by noisy restlessness, as well as more or less severe deficits of memory, general knowledge, and thinking ability.

Disorientation, bewilderment, incoherence, and perceptual and psychomotor disturbance of rapid onset appear to characterize pseudodelirium. In pseudodelirium, cognitive performance tends to normalize under amobarbital, the EEG is normal, and DST results are likely to be abnormal if a major depressive disorder underlies the transient cognitive disorder in the absence of advanced primary dementia or inanition.

In schizophrenia there is usually no alteration in the level of consciousness. The schizophrenic is usually not disoriented, but if so, the disorientation is likely to be bizarre and remote.²

The treatment of delirium requires a dual approach: etiologic and symptomatic.

Correct diagnosis of the causative agent and appropriate therapy directed at the underlying disease are essential.³ Table III gives useful laboratory tests to help in the diagnosis of delirium.

TABLE III

Helpful Laboratories to Establish the Causes of Delirium

- 1. Blood chemistries: electrolytes, blood gases, glucose levels, BUN and creatinine, liver profile.
- 2. Hemogram
- 3. Blood culture
- 4. Serology
- 5. Toxic drug screen
- 6. Urinalysis
- 7. Chest X-Ray
- 8. Electrocardiogram
- 9. Electroencephalogram
- 10. CSF examination
- 11. CT scan of head
- Others: Vitamin B¹² and foliate levels, serum protein electrophoresis, serum thyroxine and cortisol, heavy metal screen, urinary porphobilinogen and 5 hydroxy-indolacetic acid.

Symptomatic and supportive measures designed to relieve distress and prevent complications constitute the second arm of the overall approach to managing delirium; the patient's environment should be structured to avoid sensory overload and to provide social support and sensory stimulation.³ Good nursing consistent, supportive and orientingis essential.⁵ Sleep may be aided by a hypnotic, haloperidol is the drug of choice in case of extreme agitation. It is effective and relatively safe with mild anticholinergic activity. Physostigmine is the drug

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of choice for anticholinergic delirium. Hepatic encephalopathy is managed with one of the benzodiazepines which are also preferred for delirium related to alcohol and drug withdrawal.

Data Available Based on Previous Studies

The are only a few epidemiologic studies on delirium. Most of them are among elderly population.

Delirium is found in 10 to 15% of the patients in medical and surgical wards, other authors report 5 to 15%.

The incidence increases markedly at the intensive care units, open heart and coronary surgery patients, and in patients older than 60 years. It has been reported that in the intensive care units delirium can be as high as 40%. In the open heart and coronary bypass surgery patients the incidence fluctuates between 30 to 60%.³, ¹⁰ Among elderly patients the incidence is between 46 to 80%.³ Several studies on geriatric populations demonstrate that the incidence of delirium fluctuates between 16 to 80%.⁵ It is said that the incidence is 4 times greater in patients older than 40 years.⁵

The mortality rates fluctuate between 18 to 37%⁵ in general hospital studies and about 3% in a 10 year study done among patients with coronary artery bypass grafting in Duke Hospital, N.C.³, ¹⁰

Study Based on Data Found in the University District Hospital in 1984

A. Methods

All the consultations (352) answered at the Consultation Liason Service of the University District Hospital during the year of 1984 were reviewed. Data on sex, age, consultants, and consultees diagnosis was gathered. The medical records with a final diagnosis of delirium were reviewed.

B. Findings

A total of 352 consults were reviewed. Thirty nine consults had a diagnosis of delirium, corresponding to 11%. Twenty three of them were males and 16 females. The mean male age was 43.65 years, and the mean female age was 46.63 years. The younger patient was a 17 years old female. The oldest was an 80 years old male.

Fourteen of the 39 cases of delirium were younger than 40 years (36% of the 39 cases) and the remaining 25 patients were older than 40 years (64% of the 39 cases). This data seems to verify the information given in previous studies that the incidence of delirium is greater in patients older than 40 years.

The distribution by services of the 39 delirium cases found were as follow: the Department of Surgery; with 16 delirium cases consulted:

a) emergency surgery	2	
b) maxilofacial surgery	1	
c) thoracic surgery	1	
d) neurosurgery	7	
e) surgery intensive care unit	3	
f) orthopedic To	otal 16	

and the Department of Internal medicine with 23 delirium cases consulted;

a) general internal medicine		19
b) coronary unit		3
c) medicine intensive care unit		1
	Total	23

The possible etiologies of delirium mentioned in the 39 consults that we reviewed were similar to those mentioned in the literature.

The study of the medical records at the University District Hospital, during 1984, revealed the following: 12,878 admissions and 12,004 discharges.

It was found that there were no records with a discharge diagnosis of delirium, however seventeen medical records with a discharge diagnosis of Unspecified Non Psychotic Mental Disorder following Organic Brain Damage were found.

Twelve of those records were reviewed. Five were not available. Those 12 records revealed the following: 3 of those 12 patients fills the criteria for delirium. One of those 3 patients was already diagnosed as delirium by the service of Liason-Consultation. The 3 patients were male, 59, 75 and 87 years.

Seven of the twelve cases evidenced dementia, and I had a diagnosis of schizophrenia.

Conclusions

The 39 identified delirium cases correspond to less than 1% of the 12,878 admission to this hospital in 1984. Given this data we could infer that the incidence of delirium can be less than the one established in the medical literature, however there is the posibility that at the University District Hospital the cases of delirium were not diagnosed. From January to September 1984 there were no records with a discharge diagnosis of delirium even when 39 of the consults showed evidence of delirium.

It is also possible that the delirium cases can be misdiagnosed. The review of the 12 records with the diagnosis of Unspecified Non Psychotic Mental Disorder following Organic Brain Damage evidenced that 3 of those patients fill the criteria for the diagnosis of delirium. There is another possibility that even when it is diagnosed the consultee does not consider including it on a final diagnosis due to the usual transient nature of this disorder.

Considering the high morbidity and mortality rate of this condition, it is imperative that delirium be identified and treated adequately. It is recommended that a study be designed and performed in an attempt to determine the exact incidence of delirium.

Resumen: Treinta y nueve casos de delirium identificados en el Hospital Universitario corresponden a menos de 1% de las 12,878 admisiones a este hospital en 1984. Con esta data podríamos inferir que la incidencia de delirium puede ser menor que la establecida en la literatura médica sin embargo existe la posibilidad de que en el Hospital Universitario los casos de delirium no son diagnosticados.

No se encontraron expedientes médicos con el diagnóstico de alta de delirium en dicho hospital, de enero a septiembre de 1984, aun cuando 39 de las consultas evidenciaban casos de delirium.

También existe la posibilidad de que los casos de delirium estan siendo mal diagnosticados. La revisión de los 12 expedientes médicos con el diagnóstico de Desorden Mental Psicótico no específico secundario a Daño Cerebral Orgánico evidenciaban que 3 de dichos casos llenaban los criterios para un diagnóstico de delirium.

Existe otra posibilidad; aun cuando se diagnostican los casos de delirium los consultores no consideran incluirlo como diagnóstico final dada la naturaleza transitoria del desorden.

Considerando la alta morbilidad y mortalidad de esta condición, es imperativo que los casos de delirium sean identificados y tratados adecuadamente. Se recomienda un estudio para determinar la incidencia exacta de delirium.

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Multiple Myeloma Terminating in Acute Leukemia: Report of Two Cases and Review of the Literature

Genoveva Martínez-Poventud, M.D. Adry C. Fernández, M.D. Enrique Vélez-García, M.D., F.A.C.P.

Abstract: The simultaneous presentation of multiple myeloma (MM) and other hematologic disorders in the same patient although rare, is well known. However, only few reports of simultaneous MM and acute leukemia (AL) have been published. The majority of patients with MM who develop acute myelogenous leukemia have received long term chemotherapy with alkylating agents, thus, implicating the latter as a possible etiologic factor. During the past 14 years (1970-1984), we have followed 141 patients with MM at the University Hospital; only 3 (2.1%) have developed AL. Two were females, ages 48 and 49, and one male, age 33. The diagnosis of MM was based on the presence of a serum monoclonal spike, lytic bone lesions, and immature plasmacytosis in the bone marrow. All the patients received long term chemotherapy with alkylating agents for 2, 9 and 10 years respectively before the onset of AL. The presenting event in all the patients was presence of immature cells in the peripheral blood and in two of the cases, unexplained thrombocytopenia. Two patients developed acute myelomonocytic leukemia and the third erythroleukemia. The patients' clinical histories and chemotherapeutic management will be presented in detail along with a pertinent review of the literature.

Since the introduction of alkylating agents in the management of multiple myeloma, prolonged survival of many of these patients has been observed. However, since 1970 there have been several reports of acute leukemia developing in patients with multiple myeloma after receiving long-term therapy with melphalan.¹⁻⁸

Of 141 patients with multiple myeloma followed at the University Hospital during the last 14 years, we have observed the development of acute leukemia in only 3 instances. All 3 patients were on treatment with alkylating agents at the onset of the leukemic process. The rarity of this fatal complication in our experience prompted us to report these cases and to review the existing literature.

Case Reports

Case 1. A 49 years old female who developed back pain and symptoms of anemia in 1961, was found to have multiple myeloma. The diagnosis was established by the presence of multiple lytic lesions in the skull, thoracolumbar spine, ribs and pelvis, and increased immature plasma cells in the bone marrow aspirate. The patient was lost to follow up until 1967 when the back pain recurred and prompted hospitalization at the University Hospital for re-evaluation. Physical examination revealed no hepatosplenomegaly or lymphadenopathy. The skeletal survey showed severe osteoporosis, diffuse punched out lesions and vertebral fractures. The laboratory findings were: a monoclonal serum protein peak (IgG) of 2.6 g/dl and immature plasmacytosis in the bone marrow aspirate, with a hemoglobin of 7.5 g/dl. The patient was started on phenylalanine mustard, 6 mg/day for 10 days, and was subsequently maintained on 4 mg/day until 1977 (a total of 10 years of continued treatment). The patient also had other complications: bronchopneumonia, mild congestive heart failure secondary to hypertensive cardiovascular disease, and hypercalcemia with values over 15mg/dl in September 1976. The response to therapy was poor, except for improvement in general well-being, with an increase in serum IgG levels to 6 g/dl, with the lowest level attained in 1977 of 4.2 g/dl.

In March 1977, the patient complained of generalized weakness and increase in bone pain. Complete blood counts showed pancytopenia with a hemoglobin of 8.6 g/dl and a platelet count of 52,000/mm³. The pancytopenia rapidly became worse and the bone marrow aspirate was diagnostic of acute myelogenous leukemia. The patient developed fever and severe thrombocytopenia (4,000/mm³), and was started on treatment with 6-mercaptopurine, 100 mg/day. The evolution was rapid and death occurred in May 1977 of advancing disease, refractory to treatment.

Case 2. A 48 year old female with history of back pain since 1967, was hospitalized at the Mount Sinai Hospital in New York in 1969 because of urinary incontinence. During a preoperative laboratory evaluation the patient was found with a total serum protein greater than 10 g/dl. She was evaluated and diagnosed as multiple myeloma. Initial treatment with a nitrosourea (BiCNU) for 4 courses was given. The patient refused further therapy until June 1973, when she was again referred to the University Hospital. After receiving physical therapy for recurrent back pain the patient was re-evaluated and

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found with a serum protein monoclonal peak (IgG) of 7.6 g/dl, immature marrow plasmacytosis and generalized osteoporosis in the skeletal survey. She was begun on phenylalanine mustard, 14 mg/day for 4 days, and prednisone, 80 mg day for 4 days, in 28 day cycles. In spite of therapy, the condition deteriorated with diffuse bone pain. The lowest serum IgG level was 4.3 g/dl and no further complications were reported. In May 1975, sudden pancytopenia was observed and bone marrow aspiration showed a hypocellular marrow consistent with multiple myeloma. Therapy was withheld for a few days and re-started when adequate peripheral blood counts were available. In July 1975, therapy was changed to cyclophosphamide, 1 g IV and prednisone, 80 mg/day for 7 days, repeated every 28 days for 4 courses.

On January 1976, the blood count revealed severe thrombocytopenia (38,000/mm³) and a leukocyte count of 6,156/mm³ with 5% immature cells and 17% monocytes. Bone marrow aspirate was markedly hypocellular and consistent with acute myelomonocytic leukemia. Therapy for the acute leukemia was not advised in view of the hypocellularity of the bone marrow. The patient required supportive therapy with platelets and packed red blood cell transfusions. On physical examination she had developed multiple diffuse lymphadenopathy and hepatosplenomegaly. On April 1976, the patient was begun on arabinosyl cytosine, 120 mg IV, and 6-thioguanine, 120 mg, bid for 5 consecutive days monthly, for 6 courses. On November 1976, the therapy was changed to hydroxyurea, 1 g/day. The patient died on December 1976 due to advancing disease and its complications.

Case 3. A 33 year old male who in 1965 developed back pain was found with multiple myeloma and treated with local radiotherapy to a pathologic lumbar spine fracture. Due to persistence of the back pain the patient was started on treatment with phenylalanine mustard and prednisone in a monthly schedule in 1968 and referred to our institution in 1972, where the same treatment modality was continued. The patient had no complications to therapy with phenylalanine mustard and had normal blood counts and serum protein electrophoreses during the ensuing 9 years.

In October 1977, chemotherapy with phenylalanine mustard was discontinued because of anemia and leukocytosis with shift to the left in the reported blood counts. The peripheral blood smear showed abnormal, large platelets, mild leukocytosis with all the precursors represented and rouleaux formation. The bone marrow was hypercellular with increased number of plasma cells, blasts cells and promyelocytes. In the cytochemical sudies the erythrocytic precursors were PAS (periodic acid schiff reaction) positive, compatible with erythroleukemia.

The patient was treated with the COAP regimen (cyclophosphamide, vincristine, arabinosyl cytosine and prednisone) every 21 days for 5 courses; after which, the bone marrow became hypercellular, with more than 10% blast cells. The COAP regimen was then discontinued, and the patient treated with arabinosyl cytosine by continuous intravenous infusion for seven days (100 mg/M²/day) and thioguanine for 5 days (100 mg/M²

twice/day). The patient received 4 courses with this regimen and subsequently developed severe pancytopenia. The bone marrow was hypercellular with less than 5% blast forms, but with neoplastic erythropoiesis. The patient was started on treatment with 6-mercaptopurine and prednisone on August, 1978. One month later the peripheral blood counts revealed a hemoglobin of 5.8 g/dl, a platelet count of 2,000/mm³, white blood count of 5,735/mm³ with 31% blast cells. Subsequently, the patient died of sepsis and advancing disease.

Results

Three patients with acute leukemia were identified among 141 patients with multiple myeloma treated at the University Hospital during a 14 year period (1970-1984). The incidence of acute leukemia in our series was estimated at 2.1%. There were 2 females and 1 male, and the ages at the time of diagnosis of multiple myeloma were 48, 49 and 33 years old respectively. The criteria for the diagnosis of myeloma were based on the classical diagnostic triad of marrow plasmacytosis, lytic bone lesions and a monoclonal serum M-protein in the 2 female patients. Following the recognized clinical criteria of the staging system of Durie et al⁹ both female patients were staged IIIA (with high myeloma cell mass) and the male patient in stage IIA, at the time of diagnosis of the acute leukemia.

In both female patients the M-protein component was an IgG, and the three patients received long-term chemotherapy with the alkylating agent phenylalanine mustard. Case 1 was treated on a low dose daily regimen for 10 years, cases 2 and 3 with a monthly schedule for 2 and 9 years respectively. None of the three patients achieved an objective response to the chemotherapy and only one patient received radiotherapy which was administered 9 years prior to the onset of the acute leukemia.

In retrospect, the onset of acute leukemia in two of the patients was heralded by the development of thrombocytopenia and in one patient by the appearance of bizarre platelet forms. The leukemia was refractory to treatment in the three cases.

Discussion

The precise incidence of acute leukemia in multiple myeloma patients has been difficult to determine. Prior to 1970 as reported by Kyle et al, only two previous reports of acute leukemia developing in patients with multiple myeloma had been published in the United States. It is now well recognized that acute leukemia may follow long-term therapy with alkylating agents. González et al² reported that the incidence of leukemia or sideroblastic anemia in these patients occurs about 100 times more frequently than in an age-matched normal subject population. Casciato and Scott³ reviewed 54 cases reported prior to 1977, all of whom were treated with chemotherapy; of these, 21 had also received radiotherapy. Bergsagel et al4 estimated the risk of developing acute leukemia to be 19.6% at 50 months after the initiation of chemotherapy. However, the simultaneous occurence of acute leukemia and multiple myeloma

without previous chemotherapy has also been described by Tursz¹⁰ and Cleary.¹¹ In 1974, Rosner et al⁵⁻⁶ reviewed 46 cases of multiple myeloma terminating in acute leukemia and found that the majority were acute myelogenous leukemia.

Even though there is an increased risk of acute leukemia in patients treated with alkylating agents, cases of spontaneous development of this neoplasia have occurred. It is also well known that patients with one neoplasia have a higher risk of developing a second malignancy, however, it is not clear whether the simultaneous or subsequent development of acute leukemia is part of the natural history of plasma cell dyscrasias, independent of the administration of cytotoxic therapy.

A high incidence of acute leukemia has been observed in patients treated with alkylating agents. ¹⁻⁸ In general, the response to antileukemic therapy in these instances has been very poor. It is hard to explain the reasons why the incidence of this complication in our patient population is so low, only 2.1%, in spite of the fact that we have been using alkylating agents in myeloma and other conditions for a long time. Probably, this may be due to the awareness of the possibility of this complication and as a consequence of this, our custom of withholding therapy as soon as the plateau in parameters is reached.

Since 1963, phenylalanine mustard has been widely used for the treatment of multiple myeloma with objective response rates of around 40%. Several other chemotherapeutic regimens have been studied. The addition of phenylalanine mustard to these regimens has improved the response rates, however, the effects on improving survival with the cytotoxic drugs tried so far, have been negligible.

Drug-induced leukemia may be a late complication in patients with myeloma, but, since therapy with phenylalanine mustard has been proven superior in improving the response rate, it continues to be the drug of choice despite the incidence of this late fatal complication.¹²

La presentación simultánea de mieloma múltiple y otras enfermedades hematológicas en un mismo paciente, se observa en muy raras ocasiones. Se han publicado muy pocos casos en la literatura en que coexiste mieloma múltiple y leucemia aguda. En la mayoría de estos casos los pacientes presentaron la leucemia después de haber recibido tratamiento prolongado con agentes alquilantes, razón por la cual se ha implicado a estos como posible factor etiológico causal de la leucemia. Durante los últimos 14 años hemos seguido 141 pacientes con mieloma múltiple en el Hospital Universitario, de los cuales 3 (2.1%) presentaron posteriormente leucemia aguda. Dos pacientes eran mujeres de 48 y 49 años y uno varón de 33 años. El diagnóstico de mieloma múltiple se estableció por la presencia de un pico protéico monoclonal en suero, lesiones óseas líticas y la presencia de una plasmacitosis inmadura en la médula ósea. Los tres pacientes fueron tratados con agentes alquilantes por 2, 9 y 10 años respectivamente antes del inicio de la leucemia. El evento inicial en dos de los casos fue trombocitopenia, alteraciones morfológicas de las plaquetas en uno de los pacientes, y la presencia de células inmaduras en la sangre periférica. La transformación en los tres casos fue a leucemia aguda mielógena. Dos de los pacientes recibieron terapia antileucémica durante 9 y 11 meses respectivamente. El cuadro clínico de los tres pacientes se describe en detalle y se revisa la literatura pertinente.

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Gastric Emptying in a Diabetic: 99mTc Sulfur Colloid in Solid Meal

Julio V. Rivera, M.D. P.H. García Pont, M.D.

A 60 year old male was admitted on May 16, 1985 with complaints of nausea, vomiting, diffuse abdominal pain and general malaise of 10 days duration. He was known to have insulin dependent diabetes and hypertension since 1972. He had experienced similar gastrointestinal symptoms in November 1984 at which time he was found to have renal failure. He was relieved of these symptoms following the institution of ambulatory peritoneal dialysis.

On admission he was found to be pale and dehydrated but alert. Blood pressure was 150/90 mmHg, pulse 68/min. Examination of the abdomen was normal. There was no evidence of peripheral neuropathy. Ocular fundi showed advanced retinopathy.

Hemoglobin was 10.8 g/dl; leukocytes, 10,600/cu mm. Serum albumin was 3.3 g/dl; calcium, 10.1 mg/dl; phosphorus, 6.1 mg/dl; creatinine, 11.1 mg/dl. Serum electrolytes were as follows: sodium 130 mEq/L, potassium 5.4 mEq/L, chloride 91 mEq/L; CO₂, 23 mEq/L. glucose was 478 mg/dl.

An upper gastrointestinal series (Fig. 1) on May 16 showed a capacious stomach with retained food. The transit of the barium meal through the upper gastrointestinal tract was normal.

A gastric emptying study with 99m Tc in scrambled eggs on May 17 demonstrated marked delay (Fig. 2 and 4).

Intravenous fluids and insulin were given. Peritoneal dialysis was continued. On May 21 metoclopramide 10mg before meals and at bedtime was started. Abdominal symptoms ceased and the patient was discharged to out-patient clinic. Gastric emptying study was repeated on June 6 with normal results (Fig. 3 and 4).

Figure 1. Single image of gastrointestinal series shows capacious stomach with retained undigested food. The transit of the barium meal through the upper gastrointestinal tract was within normal limits.

From the Medical and Nuclear Medicine Services, Veterans Administration Medical and Regional, Office Center, San Juan, Puerto Rico and the Department of Medicine and Radiological Sciences, University of Puerto Rico School of Medicine

Gastric Emptying in a Diabetic....

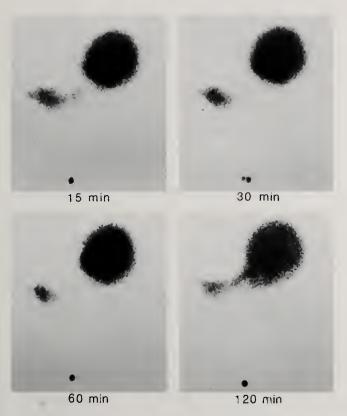


Figure 2. Serial images of gastric emptying study (99mTc-sulphur colloid in egg) on May 17 demonstrated marked retention of the meal for 2 hours.

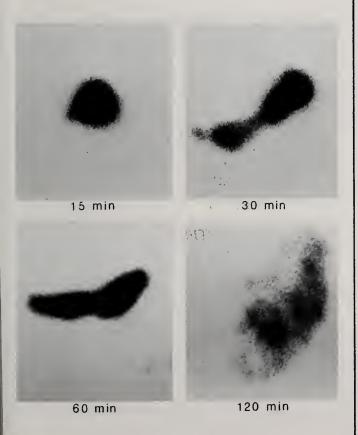


Figure 3. Second study when patient was on metaclopramide shows a normal gastric emptying pattern.

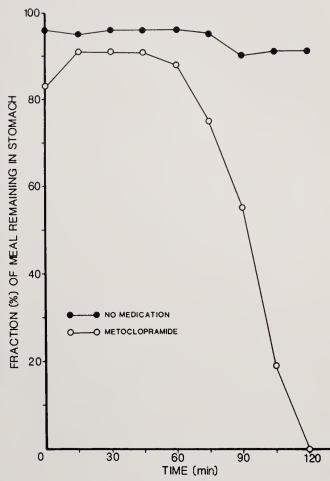


Figure 4. Fraction of remaining activity in the stomach on May 17 without medication and on June 6 while on metaclopramide.

Discussion

The transit of liquids through the stomach is governed directly by pressure gradients while the expulsion of solid meals depends principally on peristalsis. Gastric antral dysfunction may severely delay solids while sparing liquids.¹

Alterations in gastric motility and emptying are frequent and important clinical problems. Causes for delay in gastric emptying are many, including acid-peptic disease, metabolic disorders, anticholinergic and narcotic drugs, and surgical procedures. Diabetic gastroparesis, which is reported to occur in 22% of insulin-dependent diabetics, is of special interest as it may influence the control of diabetes and affect the absorption of medications.²

Although severe disorders of gastric function will usually be accompanied by symptoms such as anorexia, nausea, distension and malnutrition, the onset may be insiduous and manifestations intermittent, particularly in less severe cases. Clinical observations before and after therapeutic interventions are not reliable. Pellegrini³ has reported that about one half of cases referred with suspected gastroparesis had normal or even increased emptying.

The traditional methods for the evaluation of gastric motility and emptying have included the roentgenological observation of a barium sulfate meal, the saline-load test, the endoscopic observation of decreased peristalsis, a dilated stomach and retained food. These procedures provide anatomic observations of the gastric outlet, usually detect mechanical obstructions and provide information about the passage of liquids. Barium sulfate meals behave as liquids. Evaluation of the handling of solids by the stomach is not usually possible and these methods do not allow the serial quantitative measurements which are necessary for the assessment of therapeutic procedures.²

As in this case, quantitative observations of the transit through the stomach of a radionuclide labeled meal can provide clinically valuable information. The examination truly examines the behavior of food under physiological conditions. Observations may be made about the movement of liquids and solids simultaneously by employing appropriate tracers. 99m Tc sulfur colloid mixed with scrambled eggs or as a label for chicken livers permits observations of a solid phase. 113m In diethylene diamine pentaacetic acid may be used to evaluate the passage of liquids. The reproducibility and accuracy of these procedures has been adequately established.4 Patient acceptance is not a problem and radiation dose is smaller than required by common radiologic examinations. The procedure has been carried out successfully in children with postprandial vomiting.5

Recently similar, though somewhat more complex, procedures for the study of small bowel function have been introduced.⁶

Metoclopramide, a cholinergic drug which stimulates antral contractions has been found to be effective in the management of diabetic and idiopathic gastroparesis, but results of treatment have been variable in gastric motility problems following gastric surgery.³ In diabetic gastroparesis metoclopramide re-establishes phase III gastric activity which is deficient. Ontoward reactions to the drug do occur in 10%-20% of persons taking it and include extrapyramidal syndromes (in 1%), drowsiness and lightheadedness.⁷

We suggest that the procedure described here deserves more widespread clinical application particularly in the evaluation of therapeutic interventions, be these surgical or medical. This examination does not provide nor substitute the diagnostic information obtainable from roentgen and endoscopic examinations. The radionuclide examination is helpful in the collection of quantitative functional data on gastric function.

Resumen: Se describe la evaluación cuantitativa del vaciamiento gástrico en un enfermo con gastroparesis diabética mediante la ingesta de huevo marcado con coloide radioactivo. Se estudió el efecto del agente colinérgico metoclopramida. Sugerimos el uso de este método para la evaluación objetiva de los resultados de intervenciones terapéuticas en personas con trastornos de motilidad gástrica.

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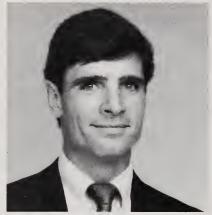


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ARTICULOS ESPECIALES

The Potential Role of Potassium in Blood Pressure Control

Siegfried Heyden, M.D.*
J. George Fodor, M.D.**

Epidemiological studies

Style and habits have considerable influence on both blood pressure levels (b.p.) and dietary potassium intake. Kesteloot et al. compared b.p. with sodium intake in Belgium and Korea. Blood pressure levels were found to be higher and sodium intake and excretion significantly higher among Koreans than among Belgians. Potassium intake and excretion were lower in Koreans than in Belgians. A significant negative relationship between potassium and blood pressure level was established, which is interesting because the drop in b.p. per millimole of electrolyte was about three times more pronounced than the positive effect of sodium. Thus, the use of potassium appears to be a possible dietary tool in the management of b.p.

Morgan et al. reviewed a study of two populations in South America. They found that different degrees of urbanization correlated with different eating patterns and b.p. levels. The more urbanized population used more NaCl and had higher b.p. The rural population still used plant ashes (potassium chloride) and retained lower b.p. Other studies on groups in primitive societies have confirmed that persons with a low salt, high potassium intake remain normontensive and have no rise in b.p. with age. Abernethy noted that low sodium diets are regularly accompanied by a high potassium intake of 7,800 mg to 11,700 mg (200 to 300 mEq) per day.

In a random sample of adult Newfoundlanders, Fodor showed evidence of a suboptimal dietary potassium intake. Potassium consumption was lower among 51 hypertensive patients (1,525 mg/day) than among 93 normotensive persons (1,750 mg/day). The minimum requirement of potassium intake was thought to be 2,000 mg/day by the McGovern Senate Subcommittee of the USA in 1977. Sodium intake among Newfoundlanders is very high, since salt fish, salt potatoes, and canned vegetables are staples of the daily diet. In this easternmost island of the North American continent the stroke rate is as high as found in the southeastern "stroke belt" extending from North Carolina to Georgia.

Other studies (in Evans County, Georgia; Baltimore, Maryland; Washington, D.C.; New Orleans, Louisiana; and Jackson, Mississippi) document the lower potassium intake among blacks in comparison to whites. Blacks in Evans County, for instance, consumed about 50% less potassium than whites, which was obviously related to their inadequates intake of fruits, vegetables, as well as to the traditionally longer cooking process whereby the intracellular potassium is removed from beef, fowl, and potatoes and discarded with the cooking water. In South Africa, a low potassium intake is associated with the lowest socio-economic class since the blacks in the upper class have the same diets as whites. A low potassium intake is usually coupled with a high sodium consumption; it is tempting to speculate that the higher prevalence of hypertension in blacks compared to whites may be partly explained by this electrolyte imbalance. The VA Study Group pointed out that the presence of a considerably reduced potassium excretion was "one of the most striking racial differences... probably reflecting a diminished dietary intake of potassium in blacks compared with whites."

In studies of six male Japanese populations, Ueshima et al. (1981) analyzed serum potassium and surveyed dietay intake by the 24-hour recall method. There was a significant negative correlation between the mean serum potassium level and the prevalence of hypertension. The serum potassium level was lowest in Akita where the prevalence of hypertension and the sodium intake were highest. However, potassium intake was also significantly higher. It was suggested that hypertension, and the low serum potassium in Akita, despite high potassium intake, resulted from the high sodium intake which

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promotes kaliuresis. Generally speaking, for people on a high sodium diet, "sodium in kaliuretic" and "potassium is natriuretic".

The relation of arterial pressure to body sodium, body potassium, and plasma potassium in essential hypertension was studied by Beretta-Piccoli et al. (1982). This clinical investigation of 91 hypertensives and 121 normal controls confirmed results obtained in more indirect epidemiological surveys. The exchangeable sodium and total body sodium increased with age in hypertensives, but not in normal subjects. On the other hand, plasma potassium concentrations, exchangeable potassium, and total body potassium correlated inversely and significantly with b.p. in hypertensive patients. These correlations were more marked in young patients. The authors suggested that changes in plasma and body potassium are important in the earlier stages of hypertension and that changes in body sodium may become importance later.

In the British Whitehall long-term epidemiological study (Bulpitt et al., 1981), 2,216 men and 1,362 women had hypertension, but were not taking anti-hypertensive medication. After adjustment for age and body mass, plama potassium was negatively associated with both systolic and diastolic b.p. A decrease of only 1 mmol/litre in women was associated with a systolic b.p. increase of 7 mm Hg and a diastolic b.p. increase of 4 mm Hg (p<0.001 for both). In men, the corresponding increases were 4 mm Hg and 2 mm Hg, both significant at p<0.05.

Experiments with humans

The first double-blind experiments with potassium chloride (KCl) in humans were reported in 1980 and 1981. An Austrian group demonstrated that the addition of 8 g KCl caused a marked drop in systolic and diastolic c.p. in contrast to a diet that was restricted in sodium and contained no added KCl. This study involved 2 weeks of crossover experiments on 21 normotensive medical students, half of whom had a family history positive for hypertension.

In England (Parfrey et al., 1981), 12 weeks of experiments with 16 hypertensive and 8 normotensive persons resulted in an evaluation of systolic and diastolic b.p. when 6 g of NaCl was added to the diet. The addition of KCl over 12 weeks resulted in a significant decrease in systolic and diastolic b.p. levels.

These results suggest that the fall in b.p. among hypertensives during the high potassium, low sodium diet was mainly due to the increased potassium intake. Return to their customary diet was associated with a marginal rise in sodium intake but a much greater fall in potassium intake, and their b.p. levels rose again.

In another publication from Austria, Skrabal et al. (1981) studied 20 normotensive students. After adding potassium and keeping total calories the same, a weight reduction of 1 kg was noticeable within 1 week. This was interpreted as due to a loss of extracellular fluid volume and was related to the direct saliuretic effect of potassium on the kidneys.

In a Japanese study with 20 hypertensive in-patients, Limura et al. (1981) observed a significant reduction of body weight, extracellular fluid volume, total exchangeable sodium and mean arterial pressure (from 114 to 103) after 10 days of potassium loading (175 mmol potassium a day for 10 days). They felt that the hypotensive effect of high potassium intake may be caused by a reduction in body fluid volume through augmentation of sodium excretion.

MacGregor et al. (1982) followed 13 patients for 2 months treatment. Their mean b.p. levels were 154 to 99 mm Hg when they were studied in an 8-week double-blind randomized cross-over study. They were treated for 1 month with either slow release potassium tablets (60 mmol/day) or a placebo without alteration of dietary sodium and potassium. For those taking supplemental potassium, their mean supine b.p. levels had fallen by 4% after 4 weeks. Their urinary potassium excretion was increased from 64 mmol/24 hours to 118 mmol/24 hours. The authors concluded that this moderate potassium intake could be achieved by using a potassium-based salt substitute together with a moderate increase in vegetable and fruit consumption.

Conclusions

From an assessment of the results it is not clear whether the relatively short duration of the experiments is an important factor. The Japanese in-patient study was terminated after 10 days, the Austrian crossover study periods lasted only 2 weeks, and the several English studies lasted between 8 and 12 weeks for each dietary change. We now must ask whether the lowering of b.p. levels in association with a high potassium diet represents a permanent change.

Such a possibility is suggested by a preliminary report by Dodson et al. (1981) indicating a highly significant diatolic blood pressure reduction in 13 of 32 hypertensive patients for as long as 9 months on a diet providing 40 to 50 mmol/day sodium and 80 to 90 mmol/day potassium. The mean diastolic b.p. was reduced from 98.3 to 85.0 mm Hg. Nothing, however, is known about the b.p. of the remaining 19 hypertensive patients.

We feel that data on dietary electrolyte manipulation shows great promise. However, final proof of the hypothesis that adding potassium to a sodium-restricted diet will have a permanent effect on elevated b.p. levels and be valuable in the primary prevention of hypertension will require further extended investigations. In addition to the background of well publicized animal experiments and a wealth of epidemiological observation, it is now time for vigorously conducted long-term intervention studies.

A bibliography is available upon written request from Dr. J. George Fodor.

"Computadoras en la Educación Médica"

Antonio Bonnet Seoane, M.D.

La enseñanza de la Medicina está en crisis. Para actualizar al estudiante con los nuevos y valiosos avances de la Medicina se experimenta con los currículos, se refuerza la instrumentación (sistemas audiovisuales) y se depura la metodología instruccional (planificación, estrategias, objetivos, etc.). Hacen falta nuevos patrones para la incubación y desarrollo del médico, quien va a ejercer en un ambiente que no es posible predecir debido a su rapidez evolutiva.^{1, 2}

A grandes males... Bueno, no es fácil adivinar cuál será el remedio, pero sí se puede anticipar que la computadora jugará un primer papel en la enseñanza médica del futuro.

La computadora es la invención más trascendental en la historia de la humanidad tanto por su capacidad para resolver problemas como por su capacidad para generar progreso. Aunque fue concebida para ejecutar operaciones aritméticas a gran velocidad, su poder principal es el manejo interno de gran cantidad de información en corto tiempo. Ya está adentrándose en la educación médica.

El rápido devenir del conocimiento médico disminuye la distancia entre el profesional y el estudiante. El acto de la graduación académica es solo un hito en la vida del estudiante. Las escuelas de Medicina tendrán que crear sistemas nuevos para mantener la capacidad del profesional sin apartarlo demasiado de sus pacientes. Ya, la Escuela de Medicina de Harvard y el Hospital General de Massachusetts, ofrecen servicios de educación por computador (MGH-CME) con cursos médicos interactivos y simulaciones clínicas. Mediante la microcomputadora y un económico adaptador a teléfono (MODEM), el médico puede ponerse al día en alguno de los temas disponibles e incluso obtener créditos en Educación Médica Contínua, Categoría I. El servicio MGH-CME aún no es económico pero es un paso importante por su bien diseñadas lecciones, elaborada estrategia educativa y diversidad de simulaciones clínicas; también porque actualiza conceptos médicos, procedimientos diagnósticos y métodos terapéuticos.³ Gracias a la computadora.

Poder Educativo y Aplicaciones de la Computadora

Si enseñar es comunicar información, la computadora será la herramienta soñada por los educadores. Su flexibilidad le permite manejar las más complicadas estraugias instruccionales. Su gran memoria dinámica acepta cualquier contenido, lo organiza, lo estructura y lo presenta al estudiante en la secuencia deseada por el instructor.

Catedrático Asociado de Fisiología, Recinto de Ciencias Médicas, Universidad de Puerto Rico Su sistema de comunicaciones facilita el mando y control por el profesor, ofrecer una variedad de formas de presentación del contenido ante el estudiante permitiendo a este interaccionar y personalizar su propio aprendizaje. También puede comunicarse con otras computadoras para formar redes de máquinas que intercambian información o comparten gigantescas bibliotecas magnéticas.

A través del sistema de comunicaciones la computadora puede controlar el funcionamiento de máquinas audio-visuales que complementan y mejoran la variedad y calidad de las imágenes. Igualmente la computadora puede "percibir" el mundo exterior, mediante sensores, que trasforman fenómenos físicos y químicos (posición, temperatura, presión, pH, etc) en códigos electrónicos que la computadora interpreta y procesa inmediatamente (en "tiempo real"). Esta tecnología, muy usada para control industrial, abre un campo exicitante en la educación médica utilizando maniquíes "sensibles" para entrenamiento en procedimientos críticos. Los experimentos con maniquíes preparados para aprendizaje y práctica de la resucitación cardiopulmonar concluyen en que el entrenamiento es más rápido y eficaz que con otros métodos.4

Estudio Independiente

Facilitar el estudio independiente es una preocupación creciente. Los currículos crecen principalmente en contenido, casi nunca en tiempo, y la presión del sistema educativo no es la misma sobre todos los estudiantes de una clase. El que no puede seguir el progreso de su clase padece presiones adicionales que se acumulan y le apartan cada vez más de sus compañeros. Así pueden perderse estudiantes porque no pueden progresar a la marcha que impone el sistema de enseñanza, aun cuando podían llegar a ser buenos profesionales si se les ayuda en sus primeros fallos.

Los cursos de autoinstrucción programada no han tenido éxito en Medicina por falta de dinamismo y la monotonía de su presentación. Las bibliotecas audiovisuales contienen mucho material educativo, películas y "video-tapes", que aún no han sido desplazados por el computador. Las condiciones son muy buenas y de alta calidad técnica, sin embargo es fácil comprobar que no atraen al estudiante. Esto se debe a que la presentación, la proyección, corre automáticamente sin tener en cuenta al estudiante, quien es sólo un observador pasivo (la interacción es nula) forzado a aprender a un ritmo prefijado, sin posibilidad práctica de detenerse para razonar, o ovalar atrás para revisar. No hay "feedback" ni seguridad de que se ha aprendido lo esperado.

La computadora (especialmente la micro) es la primera

herramienta que permite y facilita el estudio independiente. Puede utilizar el mismo material audio-visual ya existente, incorporándolo como complemento en el ambiente dinámico, reactivo e interactivo, que situa al estudiante dentro del sistema instruccional y puede ajustarlo a su ritmo personal. Al final la máquina evalua su labor y le ayuda a completar los objetivos. La eficacia del estudio independiente depende del programa de enseñanza pero requiere el uso de la computadora.

Actitudes Sociales

Se ha observado que la computadora tiende a promover actitudes sociales⁵ cuando los estudiantes se reunen a su alrededor para trabajar en grupos pequeños. Las parejas hacen sus "citas de computador" con igual finalidad. Estas actitudes son beneficiosas para el aprendizaje y merecen ser patrocinadas.⁶

Ayudas al Profesor

Los fabricantes no instalan en las máquinas ningún dispositivo instruccional. El educador recibe un sistema abstracto que debe estructurar y afinar hasta convertirlo en herramienta educativa. Existen muchos lenguajes de programación, algunos diseñados especificamente para educación. También hay programas parciales (subrutinas) que simplifican el uso de gráficos, movimiento, etc. cuando se incorporan en el programa principal.

Aunque las computadoras entraron hace tiempo en las escuelas de Medicina, aun son pocos los profesores entrenados en su programación y la producción de material para enseñanza por computador es insuficiente. Para aprovechar la potencia del computador en la enseñanza médica es necesario que muchos profesores contribuyan a la preparación de lecciones y cursos.

Este es el momento en que los llamados Programas de Autor ("authoring programs") pueden ser de gran ayuda. Son programas de computador que permiten a cualquier profesor escribir programas de enseñanza con muy poco entrenamiento y sin necesidad de aprender a programar. El profesor prepara previamente la lección en el papel según su costumbre; luego la carga en el computador siguiendo instrucciones claras y sencillas. El efecto de los primeros intentos es principalmente sobre el mismo profesor, quien descubre sus propios errores y se percata de que puede corregirlos fácilmente. Los buenos programas de autor contienen mucho ingenio y tecnología educativa, ayudan a estructurar la lección, notifican la duración de los pasajes, permiten incluir destellos ("flashes"), distribuir imágenes y texto en la pantalla usando color, intercalar preguntas etc. Son realmente instructivos y atractivos para el profesor.

Ayudas Durante la Clase

El profesor puede utilizar la computadora como ayuda en sus conferencias. Es una tecnología que está extendiendose en las escuelas de Medicina tras el éxito de las primeras demostraciones. En líneas generales consiste en utilizar la computadora para substituir la pizarra y las diapositivas de esquemas y gráficos. También para controlar la proyección de imágenes (diapositivas, films, video-tape) y producción de sonidos en la secuencia

programada por el profesor. La máquina se conecta al sistema de TV del salón y gobierna los proyectores y audio. La conferencia resulta muy dinámica cuando las explicaciones del profesor se acompañan o superponen con sonido, imágenes, animación, color, etc. incluso simulaciones fisiológicas o clínicas. Al despertar la atención se hace mejor uso del tiempo y es más fácil interaccionar con el estudiante.⁸

La diversidad de estímulos y la infinidad de formas en que se pueden combinar nos permiten vislumbrar como será el profesor y como aparecerán sus lecciones en las clases dentro de pocos años.

Métodos que Facilitan el Aprendizaje

Existe una metodología instruccional, sancionada por la experiencia, que facilita el desarrollo de unidades educativas y ayuda a evitar errores, aunque no garantiza el éxito. En líneas generales se funda en considerar cada unidad de estudio como un subsistema completo que forma parte de un sistema instruccional superior (currículo). El diseño se inicia por la definición explícita de objetivos y concluye con una prueba evaluativa específica que muestra al estudiante el resultado de su labor. El plan describe la secuencia de las presentaciones, el texto, las gráficas y los recursos que facilitan la comprensión y asimilación; como el libreto de una película de cine.9

Utilizar la computadora no autoriza a suprimir o simplificar la planificación de la lección. Por el contrario, no puede faltar un buen esquema que permitirá intercalar mejoras, corregir fallos, errores y olvidos, antes de lanzarse a codificar un programa, más difícil de analizar, interpretar y modificar.

La experiencia ha mostrado el valor de algunos métodos para aumentar la eficiencia del aprendizaje por computadora: 12

1. Individualizar o personalizar el aprendizaje.

Referir al estudiante por su nombre.

Permitirle probar y elegir distintos niveles de dificultad. Permitirle ajustar su propio ritmo; cuando pasar al cuadro siguiente, volver atrás para revisar o saltar adelante para curiosear.

Disponer de una tacla "help", por si se pierde y no sabe que hacer.

Évaluar su progreso durante el estudio y movilizar recursos adicionales cuando es necesario.

2. Combinar estímulos.

Utilizar tipos variados de presentación y distintos estímulos sensoriales apuntando hacia los pasajes complicados y difíciles. Tales como:

Letras de distinto tamaño. Destello en color ("flash") de una frase corta. Esquemas o gráficos son porciones parpadeantes y breves explicaciones. Gráficas animadas para explicar fenómenos dinámicos. Sonidos o voz (sintetizada o grabada) complementando la exhibición visual.

La combinación con diapositivas, video-tape y videodisco permite manejar imágenes de alta fidelidad y escenografía de gran realismo.

3. Retroalimentación ("feedback").

El programa debe incluir alguna reacción positiva ajustada al comportamiento del estudiante. Esta es una característica peculiar del computador. Los manuales de estudio independiente, los audiovisuales, lo intentaron sin éxito; siempre aparecían muy "inertes" ante el estudiante.

Con realimentación bien diseñada el estudiante percibe (incluso identifica) al profesor que desea ayudarle y quien cordialmente reconoce su progreso. Entonces la computadora ya no suena tan inerte, tan máquina...

Se ha encontrado que solamente la retroalimentación positiva es beneficiosa, un discreto toque de humor siempre ayuda. De igual manera, está probado que la crítica o el humor incisivo producen efectos desastrosos en la actitud del estudiante.

4. Interacción.

Es un componente que no debe faltar. Se sabe que la interacción potencia el aprendizaje. Durante la conferencia el profesor suele promover interacción en un grado limitado por el tiempo disponible y el número de estudiantes. El computador es la única herramienta educativa que puede producir interacción; en contraste con las "máquinas de enseñanza", que utilizaban el concepto de premio-sanción (no premio), basado en experimentos con ratas. Tales máquinas fracasaron hace más de veinte años; las computadora sí pueden promover interacción controlada y dirigida por el profesor.

Se han descrito seis grados crecientes de interacción¹² que se relacionan positivamente con niveles taxonómicos

de la actividad cognoscitiva:

1) Observa, mira, lee, atiende. La interacción es tan pobre como con audiovisuales.

2) Encuentra, busca y señala, elije. Por ej. trabajo con

preguntas de opción múltiple.

3) Hace, cambia, modifica, altera. Por ej. sigue instrucciones para desplazar la curva de disociación de la hemoglobina alterando la temperatura y el pH.

4) Usa, aplica, resuelve. Ej. en un simulador oftalmológico estudia un paciente, hace optometría y produce

una prescripción adecuada.

5) Construye, genera. Cuando en un simulador clínico estudia un paciente, require y analiza datos de laboratorio, radiografías, etc., evalua la información y diseña un plan de tratamiento razonado.

6) Crea, inventa. Por ej.: Introduce en un simulador toda la información original necesaria para que otros estudiantes puedan trabajar al estilo de los ejemplos para los grados de interacción 4 y 5.

Los anteriores métodos deben seleccionarse y dosificarse con discrección. El profesor que consigue sus primeros éxitos corre la tentación de entusiasmarse con los trucos que domina y perder de vista distractores indeseados que desvían o sobrecargan la atención del estudiante. Un fallo frecuente en lecciones producidas por programadores expertos pero con poca experiencia docente.

Todo producto destinado a la enseñanza debe ser previamente analizado por otros profesores y probado con estudiantes.

Formas de Utilizar el Computador

Las sesiones de estudio basado en preguntas de examen (tipo "quiz") son fáciles de organizar y programar pues utilizan procedimientos y material ya existente, propio de cada profesor. Debido a su sencillez apenas contienen interacción con el estudiante. 13

El computador muestra una pregunta de opción múltiple y pide la respuesta del estudiante. Si es correcta pasa a otra pregunta; si falla le concede otra oportunidad. El computador da la clave antes de cambiar la pregunta. Al final de cada bloque (20 a 40 preguntas) da la evaluación y algún consejo personal (bibliografía, libro y páginas a revisar, etc.), cuando hace falta.

El profesor puede coleccionar bloques de preguntas y reunir una librería de tópicos en minidiscos, fáciles de

reproducir para uso por los estudiantes.

Si las preguntas están bien seleccionadas este tipo de ejercicio es muy útil para repasar antes del examen. Cierto que contienen muy poca interacción, pero esto se compensa cuando pequeños grupos de estudiantes estudian discutiendo las preguntas.⁵, ⁶

El autor ha diseñado su propia estrategia para mejorar los ejercicios con preguntas. El primer punto es seleccionar cuestiones que por su forma y contenido se prestan mejor a discusión. Aunque toda pregunta de examen tiene valor educativo, muchas no son adecuadas para el aprendizaje. En la mayoría se puede mejorar el enunciado o proposición y/o las alternativas. El segundo punto es instruir al estudiante para que no busque directamente la repuesta correcta, sino que analice cada alternativa buscando descartarla por incorrecta. 10

En el tipo "quiz-tutor" el estudiante puede pedir comentarios del profesor para cada alternativa; solo una frase corta con alguna pista para seguir razonando, pues la pregunta pierde interés cuando se conoce la clave. La ayuda del profesor proporciona un tutorial muy beneficioso, a costa de algún esfuerzo adicional.

Las lecciones, módulos o unidades de estudio independiente en computador tratan un tópico o tema muy concreto. Incluyen objetivos, evaluación, gráficos, explicaciones, simulaciones, etc., etc., para unos 40 minutos de presentación, de contenido científico relevante para el estudiante a quien se dirige, en un programa sin fallos y a prueba de errores operativos. Se estima que esta labor requiere más den 300 horas/hombre y el producto cubre solo una parte de la lección del libro de texto. Es fácil entender porqué no hay aún ningún curso completo sino mas bien artículos dispersos sobre tópicos selectos de ciencia básica y clínica. La producción de "software" médico apenas ha comenzado, pero la labor editorial ya está en marcha, es cuestión de tiempo.

Hay unidades o módulos de entrenamiento y práctica con un propósito muy específico y limitado. Por ejemplo ejercitar una habilidad (simulador de sonidos cardíacos) o aprender el manejo y funcionamiento de un equipo complejo (hemodializador).

El "curso programado" suele utilizar un manual o libro cuyo estudio se complementa con lecciones o ejercicios en el computador. En general cubren un área trascendente y concreta (por ej. electrocardiografía)

La "simulación" se basa en algún modelo matemático o lógico con variables que representan fenómenos de la vida real. Por ej. un modelo de la circulación muestra el comportamiento de la presión arterial y ritmo cardíaco (variables dependientes) cuando cambia la resistencia periférica, se administra un fármaco o en caso de

hemorragia (variables independientes). Si las variables dependientes se comportan en el modelo en forma muy parecida a la realidad, se pueden programar las ecuaciones del modelo para obtener una simulación dinámica en el computador.

Este tipo de presentación es de gran potencia educativa cuando el estudiante puede seleccionar una variable (por ej. un fármaco) y su valor (dosis) para estudiar sus efectos.

Toda la ciencia médica cuantitativa que se explica por alguna teoría formal (farmacodinamia, mecánica circulatoria, fenómenos de membrana, vectocardiografía, etc., etc.,) se puede simular (simulación analógica) en el computador. ¹⁵ A medida que el estudiante aprende hechos y fenómenos puede utilizar el simulador para manejarlos a su gusto. como variables independientes, mientras observa los cambios en otras variables. Este ejercicio equivale a un experimento donde el estudiante descubre las leyes y reglas de la teoría, aprende por si mismo.

En la "simulación problema" el computador pone a disposición del estudiante todos los datos y recursos para manejar una situación, a veces crítica. En resucitación cardiopulmonar el computador enseña a interpretar datos vitales y tomar decisiones; después simula casos reales donde el tiempo para interpretar y decidir se hace cada vez más corto.

Las simulaciones clínicas en computador son muy variadas. Generalmente presentan situaciones que podrían ser reales en la práctica de la Medicina. Los programas no son simuladores típicos sino bases de datos médicos relacionados con una entidad nosológica. La información permanece oculta y el estudiante debe utilizar sus conocimientos previos para extraer del computador (y equipo periférico) los datos necesarios para llegar a un disgnóstico, confirmarlo, descartar otro, iniciar un tratamiento, observar la evolución del paciente simulado, etc., etc., El simulador suele disponer de "switches" que alteran la disposición de las bases de datos, así se pueden simular muchas formas clínicas de la enfermedad en diversos tipos de paciente.

El valor de las simulaciones clínicas en la instrucción médica por computador es incalculable, el ingenio en el diseño, la calidad de las presentaciones y la velocidad de respuestas del computador pueden producir un realismo (simulación icónica) que equivale a experiencia profesional. Las condiciones de alto riesgo y las enfermedades excepcionales se imitan fácilmente y pueden practicarse sin peligro para un paciente.

La demanda por simulaciones clínicas estimula a la industria del "software" que prolifera en un mercado que produce grandes ganancias. Las lecciones y cursos de presentación seria, finamente programados, planificados por equipos de educadores y médicos con gran experiencia profesional, serán la pauta en la enseñanza por computador.

Hay autores que para hacer las simulaciones más llamativas sobrecargan el escenario con riesgo de relegar los objetivos instruccionales de la lección. Así algunos aspectos importantes en la vida profesional (control de costos, manejo de la oficina, seguros, riesgos médicos, etc.), no constituyen ciencia médica y pueden interferir

con la finalidad de una simulación clínica. Parece más conveniente reservarlos para un simulador de ayuda al médico que se inicia en le ejercicio profesional.

Problemas y Asuntos Pendientes

La pobreza de conocimientos sobre el fenómeno de aprendizaje entorpece la aplicación del computador a la enseñanza. Nadie sabe como ni porqué se aprende. Los educadores aún no entienden lo que realmente hace el maestro para enseñar, y en que forma el alumno aprende. Año tras año seguimos enseñando convencidos (¿sugestionados?) de que hacemos algo importante, pero no tenemos la mas remota idea sobre el proceso educativo, ni hay una ciencia de la enseñanza que nos ayude. 12

Los educadores esperan que el computador ayude a integrar las diversas teorías y explicar los fenómenos de aprendizaje, "problem solving" y desarrollo cognitivo, para poder planificar un currículo computarizado eficaz, sobre una base científica.¹⁶

Actualmente la computadora ya puede rendir, está rindiendo en la enseñanza, aunque solo se utiliza una porción ínfima de su capacidad. Entre el elemental libro electrónico ("hacer lo mismo pero con menos trabajo") y el ambicioso simulador clínico (hacia un "amplificador intelectual") hay una gama de criterios que se materializan en un "software" que crece en cantidad y calidad. Pero aun no ha llegado el momento de la penetración profunda.

La microcomputadora está aún en evolución. La batalla industrial fuerza a la producción de nuevas máquinas, mejores para competir. Aunque todas se parecen muy pocas comparten sistemas y programas (incluso las del mismo fabricante). No es posible planificar con algo tan evolutivo.⁴

Su éxito inicial fue debido al bajo costo, gracias a la tecnología del estado sólido; pero hoy es más importante la masividad de producción, el mercadeo y los sistemas operativos. Su precio está más cerca al de un automóvil que de un juguete, pero aún así la máquina es económica y rentable cuando se pueden contabilizar sus beneficios. Instalar microcomputadoras para educación conlleva una inversión que debe planificarse muy bien. El presupuesto ha de considerar no solo las máquinas sino toda la tramoya que el escenario requiere, más el necesario soporte a mantener tras los bastidores. Comprometer un proyecto a más de 5 años es arriesgado, pero la espera pasiva será muy perjudicial.

La educación médica por computador no puede esperar a que todo el contenido curricular haya sido programaddo. Para empezar sería suficiente poder reforzar las áreas más complejas, ayudar al estudiante temporalmente rezagado y disponer de un número razonable de simulaciones clínicas.

Los obstáculos que solo dependen del material instruccional se describen como "barrera del software". 17

Los programas disponibles son útiles para promoción pero no para organizar la enseñanza formal. Los programas comerciales son costosos, reclaman derechos de autor y no pueden copiarse ni alterarse. Su envoltura trasparente permite leer un resumen del contenido y rasgar la envoltura implica la aceptación de lo que hay dentro. La cortesía de las editoriales de libros con los profesores no aplica al "software" instruccional, que puede ser compartido por miles de estudiantes. Afortunadamente muchos fabricantes de "software" médico conceden 15 días de prueba para estudiar el contenido, su aplicabilidad al currículo y a los estudiantes y la compatibilidad con las computadoras locales.

Transportabilidad es el término que indica la aptitud de un programa para correr en máquinas y/o sistemas diferentes a donde fue creado. Su importancia en la barrera del "software" instruccional ha sido el asunto central de la última conferencia de la ADCIS.¹⁸

En estos momentos la computadora, el invento más importante para intercambio de información, padece la bíblica enfermedad de Babel, complicada por una barrera de "software". Confiemos en que tan poderosa máquina nos ayude a curar sus propios males.

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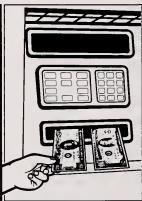
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DIAGNOSTICO ANGIOCARDIOGRAFICO



Rafael Villavicencio, M.D., F.A.C.C.* Angel F. Espinosa-López, M.D.* Lilia Roque, M.D.**

In niño de 10 años es hospitalizado para estudios diagnósticos invasivos. Tiene un retardo mental moderado e historial de soplo cardíaco desde su infancia. Nunca ha demostrado cianosis ni síntomas compatibles con insuficiencia cardíaca, el desarrollo motor es adecuado para su edad y evidencia retraso del habla.

En el examen físico se aprecian signos vitales normales con buenos sonidos cardíacos y un precordio tranquilo, sin frémito. El primer sonido es normal, el segundo sonido desdobla bien, con un componente pulmonar también normal. Hay un soplo sistólico largo, rudo, grado 3/6 en el área precordial superior. Se irradia a lo largo de ambos campos pulmonares y se ausculta particularmente bien en ambas axilas y en la espalda. No hay componentes diastólico, los pulsos periféricos son normales en las extremidades y no hay visceromegalia.

La hemoglobina y hematocrito son normales al igual que el electrocardiograma. La radiografía de torax refleja una silueta cardíaca de tamaño y configuración normal con vascularidad pulmonar también normal.

A continuación se ilustran dos vistas del angiograma realizado que permitió el diagnóstico.



Figura 1. Arteriograma pulmonar con el paciente en posición semisentada donde puede apreciarse el tracto de salida ventricular derecho (RVOT), la arteria pulmonar principal (MPA) y sus ramas derecha (RPA) e izquierda (LPA)



Figura 2. Ventriculograma derecho en posición AP.

¿CUAL ES SU DIAGNOSTICO?

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Estenosis Pulmonar Periférica

La estenosis pulmonar periférica o arterial, ya bien sea aislada o asociada a otras cardiopatías congénitas, es común. Se ha reportado una incidencia de 2-3% de todas las cardiopatías congénitas. La estenosis puede ser única, afectando bien la arteria pulmonar principal o una de sus ramas. También puede ser múltiple, afectando la arteria pulmonar común, sus ramas principales, las ramas secundarias o en las bifurcaciones de las ramas más pequeñas. Estas coartaciones pueden a su vez ser unilaterales o bilaterales.

La clasificación propuesta por Gay en 1963 ha resultado muy útil para agrupar esta malformación pulmonar.² Se dividen en cuatro tipos principales:

- Tipo I- una sola constricción, cuyo largo puede ser variable. De acuerdo a su localización se subdividen en:
 - a- estenosis de la arteria pulmonar principal o estenosis membranosa intraarterial.
 - b- estenosis de la arteria pulmonar derecha.
 - c- estenosis de la arteria pulmonarizquierda
- Tipo II- constricción del extremo distal de la arteria pulmonar principal asociada a estenosis en el origen de las arterias pulmonares izquierda y derecha. Estas a su vez pueden ser:
 - a- estenosis localizadas, de segmento corto
 b- segmentos estenóticos largos de las arterias afectadas.
- Tipo III- estenosis periférica múltiple. Las constricciones son varias, afectan solo las ramas segmentarias periféricas. Estas estrecheces por lo regular ocurren en el origen de dichas arterias segmentarias y es notable la dilatación post estenótica en cada segmento arterial afectado. La arterias pulmonar común, así como sus ramas principales izquierda y derecha son normales.
- Tipo IV- hay estenosis pulmonar central y periférica. Es un tipo III donde además están afectadas las ramas principales.

En aproximadamente 65% de los casos la estenosis envuelve el tronco pulmonar principal, su bifurcación o sus ramas principales.

Cerca de dos terceras partes de estos casos van asociados a otras cardiopatías, siendo las más frecuentes la estenosis pulmonar valvular y la comunicación interventricular.³ El ducto arterioso patente y el defecto interatrial también son frecuentes, sobre todo en los casos de embriopatía por Rubella.⁴ La estenosis pulmonar periférica también se ha reportado asociada a los síndromes de Noonan,⁵ Alagille⁶ (displasia arteriohepática) y Ehler-Danlos⁷ así como en los casos de cutis laxa.⁸

La patogenia de la estenosis pulmonar periférica se desconoce. Aparentemente múltiples factores y muchos tipos de cambios patológicos tienen el mismo resultado: estenosis del lumen de las arterias pulmonares. La elevada incidencia de anomalías intracardiacas asociadas hace sospechar que estas lesiones ocurren por alteraciones en el desarrollo. Cualquier insulto teratogénico sobre el desarrollo de estas arterias puede ocasionar una alteración de este proceso conduciendo a atresia, hipoplasia o estenosis de las mismas, algo que puede ocurrir a diferentes niveles del sistema arterial pulmonar. En los casos de estenosis pulmonar periférica por Rubella el mecanismo principal de la lesión parece ser por interferencia en la formación normal del tejido elástico. En los otros casos el segmento coartado de la arteria consiste de engrosamiento fibrótico de la íntima e hipertrofia de la capa media, resultando en una pared arterial gruesa. La estenosis pulmonar periférica asociada a estenosis aórtica supravalvular, facies peculiar y retardo mental se ha descrito como un síndrome asociado con hipercacemia infantil. 10 Sin embargo hay que considerar factores genéticos en la etiología de estas lesiones. En varias ocasiones este tipo de estenosis pulmonar fue observada en familias con historial de cardiopatías congénitas. 11, 12

Los pacientes con estenosis pulmonar periférica leve o moderada tienen un curso asintomático no importa sus lesiones sean uni o bilaterales. Aquellos casos con estenosis severa pueden manifestar disnea en reposo o tras el esfuerzo con signos y síntomas compatibles con insuficiencia cardíaca.

En los casos leves o moderados como el que ilustramos aquí tienen un primer sonido cardíaco normal que no va seguido por un "click" y el segundo sonido es de intensidad y desdoblamiento normal. Hay por lo regular un soplo sistólico-eyectivo de intensidad variable en el precordio superior que se irradia muy bien a la axila y la espalda. Cuando la estenosis pulmonar arterial es múltiple pueden oirse soplos contínuos sobre ambos campos pulmonares y espalda. 13

El electrocardiograma y la radiografía de torax son por lo regular normales en estos casos de estenosis leve o moderada. Solo en aquellos con estenosis severa es que suele aparecer hipertrofia ventricular derecha.

La angiocardiografía selectiva es la prueba diagnóstica más importante para el diagnóstico preciso de la estenosis pulmonar periférica. La localización, extensión y distribución de estas lesiones pueden visualizarse muy fácilmente con este procedimiento (figuras 1 y 2)

La estenosis pulmonar periférica aislada leve o moderada, unilateral o bilateral no necesita cirugía. Se debe hacer la excepción con aquellas coartaciones aisladas de la arteria pulmonar principal, las cuales deben ser corregidas. Con el advenimiento de materiales prostéticos modernos las lesiones estenosantes severas puden ser corregidas con buenos resultados, especialmente en niños grandes. Hay ocasiones en que la reconstrucción quirúrgica de estas arterias coartadas resulta imposible. Es por ello que la incorporación de la angioplastía de balón al armamentario terapéutico de los cardiólogos pediátricos ha resultado ser de gran beneficio para muchos pacientes considerados previamente inoperables. Cada día se

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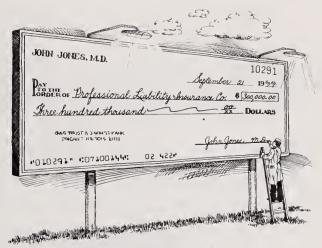
promulga más y se realiza con mayor frecuencia y mejores resultados la angioplastía de balón percutánea en pacientes con estenosis pulmonar periférica. La Es un procedimiento que se lleva a cabo en el laboratorio de cateterismo cardíaco y permite acceso a arterias que por su localización y/o extensión no son accesibles a cirugía.

El pronóstico de la estenosis pulmonar periférica está relacionado a la severidad de la obstrucción y es más o menos parecido al de la estenosis pulmonar valvular. Estos pacientes necesitan profilaxis para endocarditis.

La historia natural de estas lesiones no se conoce muy claramente, aunque se sabe que un aumento progresivo en el grado de obstrucción de estas arterias puede ocurrir. Se desconoce si esto es resultado de una discrepancia entre el crecimiento de la pared del vaso y los segmentos estenóticos. Sin embargo es muy frecuente encontrar que los gradientes de presión presente en esta malformación pulmonar arterial van desapareciendo con el crecimiento del paciente¹⁵ y que la estenosis pulmonar periférica en el adulto es rara. La explicación más lógica para esto es que la obstrucción se va haciendo menor con el crecimiento.

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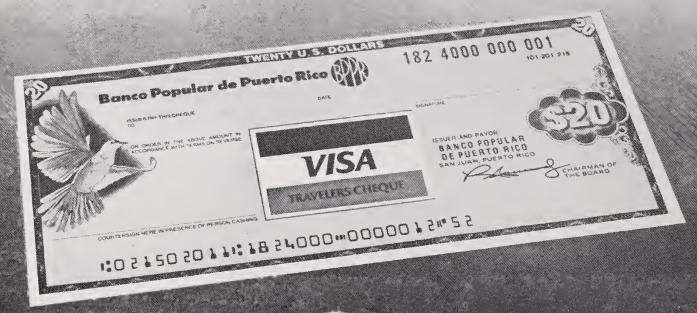
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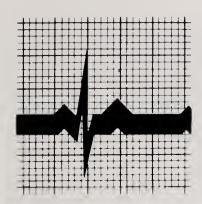




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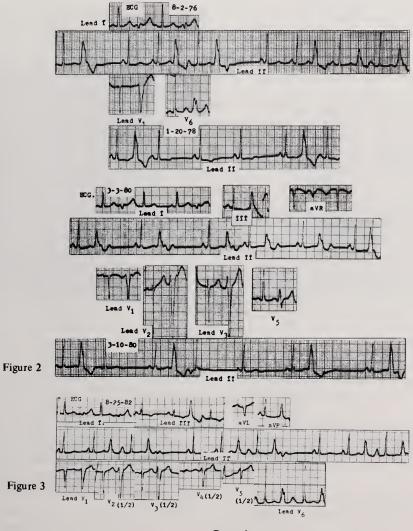
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ELECTROCARDIOGRAM OF THE MONTH

Charles D. Johnson, M.D., F.A.C.C.

This 37-year-old female complained of dizziness and palpitations. She was taking propranolol and procainamide.



Questions

- 1. What are the electrocardiographic diagnoses?
- 2. Suggest clinical diagnoses.

Clinical Diagnoses

Primary cardiomyopathy, idiopathic. Mitral regurgitation. Mitral valve prolapse (MVP).

Electrocardiographic diagnoses

Q-T interval - 0.42 S. Near QR in lead I. Sinus arrhythmia. Left atrial and left ventricular enlargement - broad P waves.

Rosenbaum Extrasystole (VE) - the ectopic beat displays a pattern of left bundle branch block (LBBB). The r wave in V_{1-5} is broad and relatively tall; the axis is inferior, near $+90^{\circ}$.

VEs: multiform; variable coupling intervals.

Interpolated- sandwiched between two conducted sinus beats; Figures 1-3 leads I and II strips. Bigeminy- first lead II strip of Figures 1 and 2. VE with retrograde P¹ in upper lead II (3rd VE), Figure 1; Figure 2, last beat in lower row; Figure 3, lead II, 4th VE.

Reciprocal (RB) or echo beat (4th normal beat) of ventricular origin (2nd VE) in the lower lead II strip of Figure 2.

In Figure II, lower lead II strip and in lead II (4th P) of Figure 3, there are atrial fusion beats - fusion between the sinus P and the retrograde P¹ waves. Retrograde concealed conduction - 2nd VE in upper lead II of Figure 1; lead III of Figure 3; lead I of Figure 1.

The RB in lead II (lower row) of Figure 2, is associated with the longest P-P¹ (1000 ms) and R-P (440 ms) intervals. The atrial fusion beats have P-P¹ intervals of 920, 900 ms and 380, 310 ms, respectively; and the retrograde P¹ waves 880, 800, 915 ms and 250, 240, 260 ms, respectively. The RB (P¹) may reset and depress the sinus node. The expected R-P/P-R reciprocal relatioship holds.

Comments

Rosenbaum, in 1969, described a type of VE that occurs usually in normal hearts. These VEs likely originate in the anterior myocardial wall of the ventricle, not far from the interventricular septum, probably from the anterior papillary muscle, and are regarded as benign (in the absence of cardiac diasease or other ECG abnormality). The Rosenbaum extrasystole: 1. resembles that of LBBB; 2. has a wide, dominantly negative QRS complex in right precordial leads, V₁₋₂, and wide, notched upright QRSs in the left chest leads, V₅₋₆; 3. the initial r wave in the right precordial leads is relatively tall and wide: 4. the mean frontal QRS forces are inferiorly, near + 90°; 5. the horizontal vector loop is counterclockwise, with a relatively prominent anterior bulge; 6. initial forces are directed more anteriorly and are inscribed very slowly. Typical LBBB manifests a: 1. leftward frontal plane axis, 2. an absent or small initial r wave, and a horizontal vector loop which is figure-of-eight and mainly clockwise.

Interpolated VEs have no compensatory pause, but the surrounding R-R interval is usually longer than the normal R-R cycle because of the subsequent P-R interval prolongation. They are favored by sinus bradycardia. Interpolated VEs with concealed retrograde (VA) conduction are due to the VE impulse penetrating back to the AV junction rendering it transiently refractory, so that the next atrial impulse is delayed in its passage through the AV junction to the ventricles to produce a prolonged P-R interval.

Retrograde atrial conduction from a VE, a P¹, is a frequent occurrence.

Interpolation and compensatory pause of VEs are closely related. In a noninterpolated VE the P wave may fall too early afterwards in the junctional refractory period to be conducted. A full compensatory pause ensues terminated by normal AV conduction of the sinus beat (note Figure 1, lead II second row and Figure 3, lead II).

A VE in a normal heart tends to show a high amplitude (usually 20 mm or more) and is clean, smooth and pointed; it is relatively narrow, usually less than 0.12 S in duration; the ST-T wave is opposite in direction to the terminal QRS deflection with a steady downward course. not horizontal, with an asymmetrical T wave; it may decrease in frequency with exercise; Lown Class 1 and 2. A VE suggesting an abnormal heart is of lower amplitude (may be 10 mm or less), markedly notched and irregular, has a slow upstroke with extreme widening (0.12 to 0.18 S), manifests an initial horizontal ST segment shelf, with concavity; the T wave is sharpely pointed, symmetrical and may be concordant with the terminal QRS delfection; it may be precipitated by exercise. Lown Class 3-5-multiform, repetitive, coupled, salvos, R-on-T; malignant. VEs secondary to digitalis intoxication occur in bigeminal pattern, show a variety of, multifocal, configurations but with a fixed interval and may have a tendency to originate from the right ventricle.

Cardiomyopathy patients, hypertrophic and dilated, usually manifest VEs, which are frequent (often more than 30 per hour) and complex (Lown grades 3-5).

MVP patients (the majority) show cardiac arrhythmias, including multiform VEs. These are usually complex and augment the risk of cardiac death.

Arrhythmogenic right ventricular dysplasia, initially described by Fontaine, arises from the right ventricle. It produces also ventricular tachycardia and VEs with a LBBB contour, often with right axis deviation and abnormal inverted T waves over the right precordial leads and right atrial enlargement. The QRS axis is less than -30° or greater tan +60°. During sinus rhythm there is complete or incomplete right bundle branch block.

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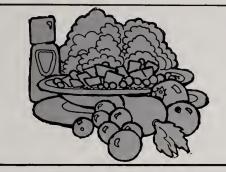
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MEDICAL ASPECTS OF NUTRITION

Body Weight Set Point Theory*

Joseph W. Kemnitz, Ph.D.**

Physiological Regulation

any physiological variables are maintained within rather limited ranges. For example, the concentration of carbon dioxide in the extracellular fluids, the concentration of sodium in blood and the temperature of the body core normally fluctuate very little in the face of challenges, such as increased muscle metabolism during exercise, consumption of salty diets and dramatic changes in environmental temperature. The functions of nearly all organs of the body are directed towards the maintenance of this constant internal environment, i.e., homeostasis.

The notion that body weight is also a controlled variable has achieved widespread popularity in recent years. According to one version of this viewpoint, individuals have a programmed level, or set point, for body weight. These set points are seen to vary among individuals so that people range from naturally lean to naturally obese. A set point model can account for the general observations that body weight usually is stable durng adulthood and that weight usually returns to this stable level after, for example, periods of gain during the holidays or after a loss incurred during illness.

Various theories of weight control have emphasized physiological, sensory, emotional and social influences on eating behavior. This article will focus only on the set point concept to explain the physiological control systems and evidence from human studies and rat models that provide the basis for this theory. Before evaluating the evidence for the existence of body weight set points, it is useful to review some aspects of engineering models of regulatory systems.

Control Systems

A general model of a control system contains several components. First, there is a controlled variable. The value of this variable is normally at a dynamic balance

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Wisconsin Regional Primate Research, Center and Department of Pediatrics, School of Medicine, University of Wiscosin, Madison, WI 53706

point and when it departs from normal, regulators are activated to oppose the change and restore the normal value. Many control systems also have a component that generates a set point signal, an input reference value, and a comparator, an element which calculates the direction of the deviation of the momentary value of the controlled variable from the set point. The regulators are activated appropriately to match the value of the controlled variable to the set point signal.

An often-used example of a set point control system is that of home temperature control. The controlled variable, inside temperature, is subject to vagaries of the weather, ventilation, etc. The set point is determined by the setting on the thermostat. The thermostat also serves as the comparator. Temperature is controlled by activating the furnace or air conditioner (the regulators) when conditions differ from this setting.

In a body weight set point model, the controlled variable is weight or, more precisely, body fat. Fat is the primary form of stored energy in the body and it makes sense that it would be regulated. The generator of the set point signal and the comparator presumably are cells in the central nervous system. The regulators are eating behavior for energy intake and physical activity and metabolic rate for energy expenditure.

Evidence from Studies of Humans

Several fundamental observations have been made that are consistent with a set point model for weight regulation in humans. For example, volunteers who reduced their caloric intake lost weight, but their energy expenditure (muscular and metabolic) also decreased as if to counter the effects of lower food intake. 1 Deliberate overeating led to weight gain, but it was usually less than would be predicted on the basis of caloric intake and was often accompanied by increased metabolic expenditure.² At the end of the controlled feeding phases of these experiments, the subjects typically overate or underate appropriately to restore their "natural" body weights.

There is considerable evidence that obese individuals often do not eat more, and sometimes less, than normals. The difficulty experienced by dieters in losing weight is also well known. Indeed, Bray has shown that as obese

patients lose weight by restricting their intake, there is a decrease in metabolic rate similar to that exhibited by normal weight subjects during food restriction.³

These observations do suggest that people defend a particular body weight. This is accomplished by behavioral means as well as by changes in metabolism. Additional information regarding these issues, especially in terms of mechanisms, is more easily and acceptably acquired by studying animal models.

Models of Obesity

Much of the current thinking regarding body weight set points derives from experiments with laboratory rats. It has been recognized since the end of the last century that damage to a part of the basal forebrain, the ventromedial hypothalamus (VMH), is associated with overeating and obesity. Kennedy, after observing rats with experimentally produced lesions in this region, suggested that the primary consequences of this damage is an elevation of the regulated level of body fat.4 Change in food intake was seen as an attempt to achieve an obese level. In other words, the rats became fat not simply because they overate, but rather they overate to become fat. Evidence for this suggestion included the observation that overeating persisted only until weight stabilized at the elevated level. Other investigators demonstrated later that overeating could be reinstated by starving the animals down to a lower weight level. Conversely, overeating could be blocked by making the animal obese by other means prior to making VMH lesions.5

Rats with VMH lesions display abnormalities other than obesity. These include marked overeating of goodtasting diets and an absence of a hypermetabolic response to increasing weight.^{6, 7} These are not typical characteristics of obese humans. Partly for these reasons, investigators are now relying more on other models of elevated set point, such as the genetically obese Zucker fatty rat, which is more like an obese human in these respects.^{6, 7} Some monkeys develop obesity spontaneously and seem to share several characteristics with obese humans.⁸ Studies of monkeys are expected to provide valuable insights into human weight regulation.

Models of Leanness

Kennedy reasoned that if damage to the VMH reset the fat control system to a higher value perhaps lesions in another area could produce regulation at a leaner level. He suggested that the lateral hypothalamus (LH) was a likely candidate for this function, because lesions in the LH had been shown to disrupt feeding.⁹

Powley and Keesey systematically investigated the possibility that LH lesions reduced the regulated level of body weight. They found that immediately after hypothalamic surgery rats greatly reduced their food intake for several days and, in some cases, stopped eating altogether. Normal levels of food intake returned, however, and the rats then chronically maintained their weight at a subnormal level. Reducing body weight prior to surgery attenuated or eliminated the effect on food intake but did not influence the chronic reduction in body weight. In subsequent experiments, it was demonstrated

that following periods of force-feeding, LH rats would still decrease their voluntary intake until they achieved or re-established a lower level of weight maintenance.^{11, 12} Following lesions of the LH, rats behaved, in fact, as if their set point for body weight regulation had been lowered.

Amphetamine and fenfluramine are two drugs that have been used to suppress appetite. Both of them exhibit decreased effectiveness with repeated administration. This has traditionally been explained on the basis of decreased sensitivity of drug receptors or increased degradation of the drug. Levitsky and coworkers recently examined a third possibility: the efficacy of these drugs to reduce hunger might be dependent upon body weight.¹³

This hypothesis was tested in a manner similar to that used to evaluate primary effects of LH lesions. In one set of experiments, rats were allowed limited access to food until their body weights were reduced by about 20%. When drug treatment was initiated, these rats did not display anorexia, but rather they ate approximately normal amounts of food while maintaining reduced weight. Non-reduced rats, on the other hand, ate less for about two weeks and lost weight. Their food intake then returned to normal and their weight was stable at the same lower level as the pre-reduced rats. In another experiments, rats that had lost weight during drug treatment were forcefed until their weight was back to control levels while drug treatment was maintained. When forcefeeding was stopped, the rats ate less until their weights returned to the previous drug-induced level of maintenance. In all experiments, when drug therapy was terminated, the rats increased their food intake until normal body weight was reinstated.

These data strongly suggest that the primary effect of the drugs, as well as that of LH lesions, is upon body weight, not appetite. Changes in eating behavior represent an effort to adjust the level of maintained body weight. A clear implication of these observations for clinical practice is that weight loss induced by drugs will likely be reversed when the drug in withdrawn.

Changing Set Points

Set points need not be invariant. Just as a home thermostat setting may be adjusted, the body weight set point can theoretically be shifted. For example, the annual increase in food intake and body fat displayed by hibernators prior to the period of torpor may represent a "sliding set point" mechanism. Similar shifts in set point have been implied to result from changing hormone levels associated with pregnancy and lactation. Frolonged overeating of high fat diets also can lead to an elevated set point. Exercise also may well contribute to alterations in set point.

Cognitive and External Factors

Garrow has forcefully argued that weight regulation in rodents is so unlike the human condition that it is inappropriate to extrapolate conclusions from these studies to man. We are exposed to a great variety of highly palatable foods and are subject to considerable social pressures and habits with regard to our eating behavior.

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Although Garrow does not deny the existence of internal cues for maintaining a particular fat reserve, he feels that in man these are overridden by cognitive and external influences. Anorexia nervosa and bulimia are disorders that represent extreme examples of high-level control of eating behavior in humans. Garrow's viewpoint does not negate the value of understanding the basic internal controls in lower animals, and the interaction among levels of control in complex animals, such as primates, represents a challenging area of investigation.

Summary

The application of the set point model to the study of weight regulation has provided a conceptual framework in which many experimental and clinical observations can be incorporated, and it has been useful for indicating critical experiments to be done.¹⁹ It should be remembered, however, that weight regulation can be achieved by feedback systems that do not contain a set poing signal and that demonstration of phenomena cosistent with a set point system does not necessarily prove its existence.¹⁹, ²⁰ Considered application of the model, with an appreciation of both its usefulness and its limitations, will further our understanding of energy regulation.

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MEDICAL SPECIALTIES SPECIALTIES NEWS



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EMERGENCY ANGIOPLASTY VS. FIBRINOLYTIC THERAPY

Emergency Balloon angioplasty has better short-term functional effects than emergency fibrinolytic therapy, according to University of Michigan researchers.

The results from a trial in 56 patients with acute MI who were randomized and treated with either percutaneous transluminal coronary angioplasty (PTCA) or intracoronary streptokinase (ic-SK) were reported.

While intracoronary streptokinase opened the coronary arteries as effectively as angioplasty—84 percent and 82 percent, respectiveley—the ic-SK patients had more residual stenosis than PTCA patients, says William W. O'Neill, M.D., Assistant Professor of Medicine, University of Michigan Medical Center, Ann Arbor.

After complete reperfusion, residual stenosis was 86 percent in ic-SK patients and 3 percent in patients undergoing PTCA. This difference between the 2 groups may have accounted for differences in their benefit from reperfusion.

PTCA significantly improved patient's ejection fraction whereas thrombolysis did not. Seventy percent of PTCA and 20 percent of SK patients had incrased ejection fraction by more than 0.05 between contrast ventriculography studies done before and about 7-10 days after treatment. PTCA-treated patients' ejection fraction improved by an average of 0.08. Their left ventricular function continued to improve for several months.

Similarly, more of the ic-SK patients re-occluded than patients who were treated with PTCA. Both groups of patients were reperfused within an average of 3-4 hours of the onset of their MI.

"The short-term effect of PTCA is better," Dr. O'Neill says. Thrombolysis patients had significantly more thallium reperfusion defects than PTCA patients.

Thrombolysis does not solve the primary problem; high-grade residual stenosis may play a significant role in

inhibiting the return of ventricular function after reperfusion.

Therefore, Dr. O'Neill says, the best treatment strategy may be emergency thrombolysis followed quickly by PTCA.

HEART OF THE ATHLETE

Recognizing the athlete who may have a cardiovascular problem continues to be of critical concern to cardiovascular specialists.

Michael H. Crawford, M.D., Professor of Medicine at the University of Texas Health Science Center, San Antonio, discussed his experience with diagnosing and assisting athletes who have or may develop a range of heart ailments, including sudden death.

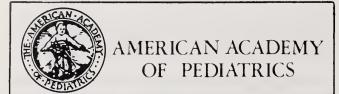
Dr. Crawford has had an interest in the heart of athletes for the last 8 years. In that time, Dr. Crawford has had patients from professional sports as high school and college athletes. "We get several types of problems in the athlete," he says. Dr. Crawford categorizes these heart-related problems into 3 basic categories. The first problem area is the heart murmur, which is very frequent. The cardiovascular specialist, according to Dr. Crawford, must make a decision if the murmur is the result of training or heart disease.

A second problem area for Dr. Crawford is the abnormal EKG. As in the case of the heart murmur, this is a difficult decision because many athletes have abnormal EKGs due to physiological changes from training. An example of how sports and training can affect the heart is the resulting enlargement of the heart. This enlargement can sometimes be as much as twice the normal size. This enlargement, which Dr. Crawford refers to as the "super normal" heart, poses a problem for the cardiovascular specialist. Is the enlargement normal or not?

The third problem area is sudden death in athletes. Dr. Crawford says this creates more and more pressure to screen athletes, the difficult task of weeding out patients with a propensity for sudden death. However, under specific circumstances there are patients with a heart murmur or abnormal EKG that should be allowed to be athletes. Dr. Crawford believes it is necessary to educate physicians so these patients with non-critical heart problems have the opportunity to be athletes, but the diagnosis must be correct. For example, Dr. Crawford says that mitral valve prolapse is very common (10 percent in females and 3 percent in males). But mitral valve prolapse is often diagnostically confused with hypertrophic cardiomyopathy a much more dangerous condition, which is the leading cause of sudden death in young athletes. "It is crucial to distinguish the two, Dr. Crawford says. The best way according to Dr. Crawford, is to use the echocardiogram.

The current debate in athletic physiological performance is what is the first limiting factor: the heart or the skeletal muscles? Dr. Crawford says the controversy has not been settled yet. Dr. Crawford believes the best exercise for the heart is isotonic exercise, such as running. Isometric exercise, where muscles contract but do not

move the body, is not good and places stress on the heart, Dr. Crawford says. But he cautions that in isotonic exercise it is crucial to train and work gradually.



PEDIATRIC BREAKTHROUGH: TRACHEAL INSTALLATION OF SURFACTANT PRIOR TO FIRST BREATH OF LIFE PREVENTS RESPIRATORY DISTRESS SYNDROME

Medical researchers have found an effective way to combat neonatal respiratory distress syndrome—a condition that causes sickness and death in very premature infants.

By being ablet to supply —prior to the first breath of life—missing surfactant at the air-liquid interface of the neonate's upper airways, survival rates are increased. The reasons: aeration is facilitated, surfactant will be evenly distributed to small airways and alveoli, the lungs will be stabilized, and gas exchange will be enhanced.

Surfactant is a substance produced by the lungs and is much like a film. Its function is to lend stability to the lungs. Ten percent of those infants who lack surfactant and contract respiratory distress syndrome die. More importantly, though, is the morbidity the syndrome can cause: permanent brain damage, central nervous system impairment and eye problems.

Researchers from the University of Toronto and the University of Western Ontario, reporting in the August issue of *Pediatrics*, conclude this treatment is a valuable addition to current management of the very preterm infant (less than 30 weeks of gestation).

In their randomized clinical trial, 39 of 72 infants (all 72 born at a gestational age of less than 30 weeks) received 3 or 4 mL of surfactant, prepared from the lipids extracted from calf lung lavage. The treatment resulted in a significantly improved gas exchange during the first 72 hours of life.

Of the 39 treated infants, only one died during the neonatal period, whereas six of the control infants died during the same period. In addition, only three of the 39 treated neonates contracted pulmonary interstitial emphysema, compared with 13 of the 33 control infants.

On the average, the researchers reported, the arterial/alveolar oxygen tension ratio was 0.15 higher for the treated infants, and only about half as much oxygen had to be supplied. In summary, they said that those infants who received the surfactant had less respiratory distress syndrome, both in incidence and severity.

Surfactant Given Before "First Breath"

To administer the surfactant, the infant's chest was gently compressed at birth in an attempt to mechanically delay an effective "first breath of life" until the substance had been supplied. The neonate was immediately taken to the resuscitation table, and after careful suctioning of the oropharynx, was intubated.

The actual installation of the surfactant (or air for the control infants) was carried out by a member of the perinatal team, who would not be involved in the care of the infant for the next 5-6 days. Following two or three manual inflations with a bag, the infant was returned to the resuscitation team. The ongoing care was identical for treated and untreated infants, and conformed to the standards fo the neonatal unit.

Goran Enhorning, M.D., who headed the study, notes that respiratory distress syndrome is the single most common problem for these very premature infants. He and his colleagues maintain there may be immediate, as well as long-term, humanitarian and economic benefits (reduced length of stay in a neonatal intensive care unit) to the prevention of respiratory distress syndrome.

"We did not anticipate a measurable reduction in mortality. However, there clearly was a difference, when taking into account that the two deaths in the group of 39 treated infants were unrelated to severe respiratory distress syndrome, whereas four of the seven deaths in the control group were due to severe hyaline membrane disease and its complications," the researchers said.

The clinical trial was carried out at Women's College Hospital in Toronto, whose neonatal unit is directed by co-researcher Andrew Shennan, M.D., the pediatrician involved in the study. Women's College Hospital is an institution where women with high-risk pregnancies are referred from several obstetrical departments with a total of 55,000 deliveries a year.

WEARING RETROREFLECTIVE MATERIAL CAN REDUCE PEDESTRIAN INJURIES

When children wear retroreflective material on jogging suits, jackets, Halloween costumes, backpacks and bicycle helmets, visibility of the children by motorists increases by as much as 175-760 feet. And that often is the difference between a safe journey or a trip to a hospital emergency room.

Thus, the American Academy of Pediatrics' (AAP) Committee on Accident and Poison Prevention strongly recommends the use of such material when children are walking or bicycling at dusk or after dark. It estimates that pedestrian injuries, which account for 1,500 child and adolescent deaths a year in the United States, could be significantly decreased by wearing retroreflective material.

"Experience with the use of retroreflective tags on outerwear in Sweden has shown that nighttime pedestrian deaths can be cut by 25 percent," the Committee writes in a policy statement issued in the August issue of AAP News.

More than 60 percent of pedestrian-auto accidents occur late in the day when light is fading or absent. Past research has shown that pedestrians overestimate the

distance at which they are visible to a driver. Conversely, studies of these accidents have shown that 85 percent of the drivers did not see the victim in time to avoid the collison. In fact, half were unaware of the pedestrian until contact.

The Academy reminds parents to tell their children to walk facing traffic— since more than two-thirds of pedestrian fatalities occur while the victim is walking with traffic. And the use of retroreflective clothing by pedestrians and reflectors by cyclists are not substitutes for sound parental judgment in determining when to allow children on the road after dark or at dusk.

CORPORAL PUNISHMENT IN SCHOOLS: WORKING OUT ALTERNATIVES

It is no secret that many organizations oppose corporal punishment in schools because it is ineffective in maintaining order and has the potential for serious injury.

The American Academy of Pediatrics (AAP) suggests that a dialogue between parents, teachers, school officials and pediatricians would be useful in discussing what the alternatives to this problem should be.

"Starting points for discussion include the abolition of corporal punishment, the use of time-out rooms in schools, restriction of privileges and the delayed participations in extracurricular activities," says Joseph Zanga, M.D., chairman of the AAP Committee on School Health and a Richmond, Va. pediatrician.

In addition, Dr. Zanga stresses the need for this forum to discuss the use of positive reinforcement towards good behavior as an alternative to striking a child.

"Let troublemakers know you reward good behavior. Giving the 'gold star' for simple, acceptable classroom behavior works for young students and is a useful item to discuss," Dr. Zanga says.

Currently, the AAP condemns any form of corporal punishment in schools and seeks its legal prohibition in all states.

SEAT BELTS IN SCHOOL BUSES: A LONG-TERM MESSAGE JUSTIFIES THEIR IMPLEMENTATION

Nearly 15 million school children step into school buses in the United States. Since all 50 state require the use of infant car seats, and many states mandate the use of seat belts by older children—ins't it about time we also considered protecting schoolkids in buses?

That's why the American Academy of Pediatrics (AAP) is asking for changes in school bus safety standards. "The reasons, however, are much deeper than just keeping children safe while in transit to and from school," says Joseph Zanga, M.D., head of the AAP's Committee on School Health. "We want the next generation of children to learn to be properly secured in any moving motor vehicle."

Based on a review of extensive motor vehicle data, the Academy supports the following changes regarding school bus safety:

- Seat belts should be required on all newly-manufactured school buses regardless of their size and the number of pupils transported.
- Seat backs should be elevated to 28 inches. This is four inches above the height now mandated by federal regulations and will support and cushion a child's head and back.
- All seat backs and tops should be padded with firm materials that adequately absorb impact. The padding should completely cover the entire rear of the seat, in addition to the top rail.
- The padding should also be placed on all stanchions and "modesty" panels. Seat construction should be designed to eliminated sharp or unyielding objects that could cause or worsen injury.
- Adequate and appropriate bus driver training should be mandatory in all school districts and should include a provision for health screening on a periodic basis, including vision and hearing tests.

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LEUKEMIA LINKED TO RADIUM GROUNDWATER CONTAMINATION

Groundwater contaminated by radium may be a contributing factor for leukemia in human populations, according to a report in JAMA.

Gary H. Lyman, MD, MPH, of the University of South Florida in Tampa, and colleagues studied groundwater samples from private wells in 27 Florida counties. They report that 12.4 percent of all samples exceeded maximum contaminant levels established by the US Environmental Protection Agency for both total radium and radium 226. Based on numbers of contaminated samples, ten counties were designated as high exposure and 17 as low exposure.

"A significant difference in adjusted leukemia incidence was observed between high-exposure counties and those with low levels of radium groundwater contamination," the researchers say. Compared with low exposure counties, the incidence in high exposure counties was one and one-half times greater for total leukemia and two times greater for acute myeloid leukemia. People living in counties with the highest levels of radium had nearly three times the risk for leukemia, the researchers add. The number of deaths from the disease was also greater in high-exposure areas.

"All ten counties in the high exposure category had adjusted leukemia incidence estimates in excess of that for the state as a whole compared with six (35 percent) of the 17 low exposure counties," the researchers say. The incidence of total leukemia and acute myeloid leukemia in high exposure areas was significantly greater than that of low exposure areas and that of the state as a whole, but there was no significant difference between incidence in low exposure areas and the entire state.

"Human leukemia is an index disorder for environmental radiation effect because of its low natural incidence, the high radiosensitivity of myeloid stem cells and the short laten period," the researchers say. They add that almost 85 percent of all radiation-induced leukemias occur within 20 years of exposure, with the greatest risk observed within five to ten years.

Samples in the study were taken from phosphatebearing regions in Florida known to contain uranium and, consequently, radon and radium. Florida has one of the largest deposits of phosphate ore in the world, and part of this lies near the water table aquifer in the southwest part of the state. The researchers say it is unclear whether the radium in the water samples is a result of natural processes or of past and present mining operations.

Although their study cannot be used to prove a cause-effect relationship between radium in groundwater and incidence of leukemia (other environmental factors and family history were not taken into account), the researchers recommend that these residents use the public water supply, which is less likely to be contaminated than private wells. They also conclude that if other studies confirm their results, actions directed at limiting groundwater contamination will be necessary.

JAMA August 2, 1985

ASPIRIN PREVENTS KAWASAKI COMPLICATIONS

Coronary aneurysms, which can cause heart attack and death in children with Kawasaki disease, may be prevented by high doses of aspirin. The new finding is documented by a study reported in JAMA.

Gideon Koren, MD, and colleagues of the University of Toronto compared coronary artery involvement in two groups of children with Kawasaki disease. Thirty-six children received acetylsalicylic acid 80 to 180 mg/kg/day and 18 did not. (Fever in the 18 nontreated patients was controlled mainly by acetaminophen.) "There were significantly more cause of coronary involvement in the nontreated group (50 percent) than in the salicylate-treated group (16.6 percent) and of coronary aneurysms (39 percent vs. 3 percent)," the researchers report.

"Although salicylates have the potential advantage of providing both antiinflammatory and antiplatelet effects in Kawasaki disease," say the researchers, "their ability to prevent coronary aneurysms has not been documented in the past." The disease most often occurs in children between the ages of 6 months and 4 years. Symptoms include fever, sore throat, redness and swelling of extremities, rash and swollen lymph nodes. It remains a difficult disease to diagnose, and the cause is unknown.

The researchers add that while fever is present, the absorption of salicylates is hindered, so it is important to maintain a high dose during that time. As fever subsides and absorption improves, the dose may have to be adjusted to avoid systemic toxicity. Because of the frequent delay in diagnosis, high-dose salicylate treatment may likely be postponed. The researchers caution against this: "Based on our findings, it is conceivable that the risk of not treating the disease during the febrile phase far outweighs the potential risks of high-dose serum concentrations of salicylates, which can be monitored daily."

Commenting editorially, David M. Bell, MD, of the University of Tennessee, Memphis, says the study by Koren and colleagues presents important new data regarding a perplexing disease. He describes what is known about Kawasaki disease: that it was first described in the 1960s in Japan, and that children of Asian ancestry have the greatest risk, followed by blacks, then whites.

The disease is most likely to occur in late winter or early spring, and there is no evidence of person-to-person contact or of a common source of exposure.

"It has become unusual in modern medicine for a serious, presumably infectious disease to defy virtually all efforts at elucidation of its etiology and pathogenesis and to leave unanwered, after two decades, so many questions about therapy and prognosis," Bell observes. He says physicians can help research efforts by reporting cases promptly to the Centers for Disease Control through their local and state health departments so that trends can be monitored and further investigation undertaken.

JAMA August 9, 1985

DIAGNOSTIC, TREATMENT GUIDELINES FOR CHILD ABUSE AND NEGLECT: AMA

Guidelines aimed at helping physicians diagnose and treat various forms of child abuse and neglect are offered by the AMA Council on Scientific Affairs in JAMA.

Each year more than 1 million children are seriously abused by their parents, guardians or other adults, the Council report states. Of those children, between 2,000 and 5,000 die as a result of their injuries, the report adds.

"Children with injuries inflicted on them by their caretakers are difficult for physicians to treat," says Douglas A. Sargent, MD, JD, chairman of the council panel that prepared the report. "As we try to diagnose and treat them, we have to struggle with our own feelings, hardly able to believe that parents could savage their children, yet bring them to us for repair."

Under state laws, physicians must now report suspected cases of abuse and neglect. They are afforded legal immunity to protect their reporting but face legal sanctions for failure to report. Thus, the guidelines hold promise of help not only for abused children and their disturbed caretakers but for physicians as well.

Several identifying factors for families and children at risk for abuse are listed in the report. Vulnerable families include those that are socially isolated, that suffer drug and alcohol abuse, and that have parents who strike one another or in which the parents were abused themselves as children. Vulnerable children include those who were born prematurely, have adolescent parents, were hospitalized for a prolonged period at birth, and are colicky.

Signs of physical abuse include bruises and welts to various part of the body, patterned burns, certain types of fractures, lacerations and abdominal injuries. Signs of sexual abuse include venereal disease, recurrent urinary tract infections, vaginal discharge, and lax rectal tone. Signs of emotional maltreatment include failure to thrive, apathy or depression and delays in physical development.

Also included are guidelines aimed at schooling physicians on how to interact with children and families in suspected cases. When interviewing the child, for example, physicians should conduct the interview in private, explain the purpose of the interview to the child in language appropriate to the youngster's age, and acknowledge the child's distress and lack of fault. Physicians also should advise parents of the legal obligation to report suspected cases, explain further

actions that may be required, answer questions honestly, and attempt to be objective.

The report also advises physicians to expand their roles beyond detection, diagnosis and treatment. "Physicians can participate in the primary prevention of child abuse as well," the report says. "Expanded well-baby care, augmented information and education, and referrals to community resources may be provided for 'high-risk' parents. Physicians also may participate in changing hospital childbirth procedures to facilitate parent-infant bonding and support early education in child development and care."

Other preventive strategies should be aimed at reducing the burden of child care, family isolation and long-term consequences of poor parenting. "Increased access to health and social services for all family members is another goal of any prevention effort," the report concludes.

JAMA August 9, 1985

DEMENTIA MORE COMMON IN WOMEN, OLDER PERSONS

The incidence of severe senile dementia of the Alzheimer's type increases with advanced age and has a higher prevalence among women, according to a study in the August Archives of Neurology. Bruce S. Schoenberg, MD, PhD, of the National Institute of Neurological and Communicative Disorders and Stroke, and colleagues studied the prevalence of severe dementia among residents of Copiah County, Mississippi. Of nearly 24,000 residents, 80 had severe dementia, and 35 of these were in institutions. Incidence rose from 1 percent among persons aged 40 and older to 7 percent in those aged 80 or more. Prevalence rations for females were about twice as high as for males, the researchers say, noting that prevalence is a function of both incidence and survival. "The major magnitude of this debilitating disorder demands important attention as the elderly segment of the United States population continues to increase in size," they say.

ZIMELDINE FAILS TO IMPROVE MEMORY IN ALZHEIMERS' PATIENTS

Zimeldine, a drug that has been shown to reverse the acute adverse effects of alcohol on memory function in normal volunteers, does not seem to be beneficial for persons with Alzheimer's disease. Neal R. Cutler, MD, of the National Institute on Aging, and colleagues tested the drug on four Alzheimer's patients in a double-blind, placebo controlled, cross-over study. Their results are reported in the August Archives of Neurology. "Under conditions during which both intended pharmokinetics and expected biochemical effects were demonstrated, no effect of zimeldine on memory function or reaction time...was found," the researchers say.

ADOLESCENT DRUG USE PRIME CAUSE OF MISBEHAVIOR

Marijuana use may be the primary cause of academic

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underachievement; acting out behavior such as theft, vandalism, or physical violence; unpredictable mood changes; apathy; or chronic fatigue, assert researchers writing in JAMA. Richard H. Schwartz, MD, and Richard Hawks, PhD, of Children's Hospital National Medical Center in Washington, D.C., and of the National Institute on Drug Abuse in Rockville, Md., suggest that primary care physicians be alert to signs of drug abuse among adolescent patients and perform urinalysis when abuse is suspected. "The physician possibly can help an admittedly reluctant patient seek counseling if marijuana use is confirmed by a urine analysis test positive for cannabinoids," they say.

JAMA August 9, 1985

NEW TREATMENT FOR SYMPTOMS OF MENIERE'S DISEASE

An effective new treatment for the vertigo and tinnitus (ringing in the ear) associated with Meniere's disease is described in the August Archives of Otolaryngology. Milo Fradis, MD, and colleagues from the Haifa Medical Center in Israel report that intratympanic injection of lidocaine hydrochlorides used with 28 patients offered immediate improvement in vertigo for 82 percent of the patients and improvement in tinnitus in 67.8 percent. As small control group offered a placebo reported no relief. "The procedure is without the hazards of the intravenous injection of lidocaine, and can be done by every otologist, even in clinic practice," the researchers say.

EXERCISE WITH WEIGHT LOSS LOWERS CHOLESTEROL

Exercise is most effective in reducing blood levels of cholesterol when accompanied by weight loss, according to a report in JAMA. The report is based on data from 95 studies conducted between 1955 and 1983 that measured changes in cholesterol associated with exercise training.

Zung Vu Tran, PhD, of the University of Colorado, Boulder, and Arthur Weltman, PhD, of the University of Virginia, Charlottesville, report that serum levels of lipid and lipoproteins significantly decreased following exercise training when body weight remained stable or decreased. The opposite effect was noted when exercise was accompanied by weight gain, although this change was not statistically significant.

"Where body weight did not change, cholesterol and low-density lopoprotein-cholesterol (LDL-C) levels decreased significantly (7.3 mg/dL and 3.3 mg/dL, respectively)," the researchers say. "Where body weight decreased, cholesterol and LDL-C levels also decreased significantly (13.2 mg/dL and 11.1 mg/dL, respectively). However, with body weight increase, cholesterol and LDL-C levels increased by 2.9 mg/dL and 3.0 mg/dL, respectively."

The researchers conclude that if maximum decreases in blood levels of cholesterol and LDL-C are desired,

persons engaging in exercise training programs should strive to maintain their body weight or lose weight. They note that while the relationship between physical exercise and serum lipid and lipoprotein levels has not been definitely established, many researchers have reported favorable effects. They add that change in subjects' body weight during exercise training has been recognized as an important confounding variable in these studies.

JAMA August 16, 1985

SUICIDE MAY HAVE GENETIC LINK

Predisposition for severe depression and suicide may be passed from one generation to the next, according to a study of the Amish reported in JAMA.

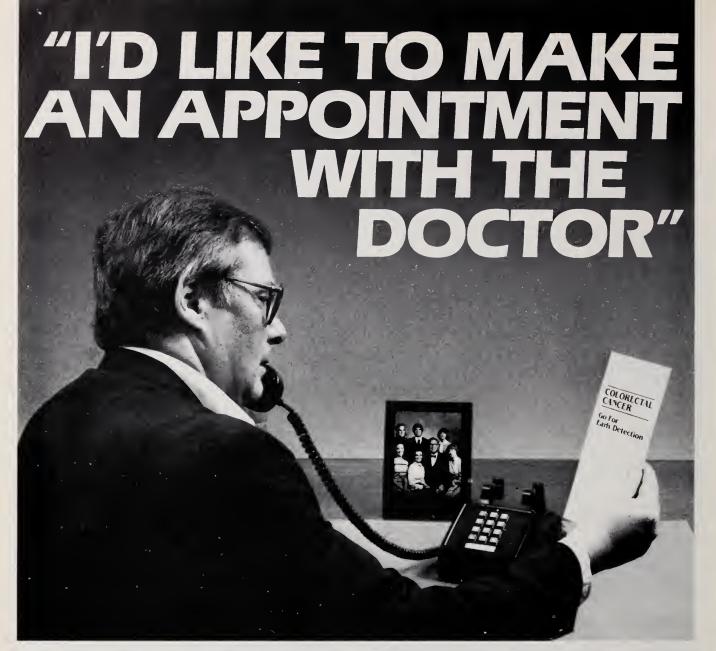
Janice A. Egeland, PhD, and James N. Sussex, MD, of the University of Miami School of Medicine studied the incidence and circumstances of suicides that occurred during a 100-year period in a community of Old Order Amish living in southeastern Pennsylvania. Because marriage occurred within the community and because the Amish way of life does not have the economic and social stresses often associated with suicide, this population provided an opportunity to evaluate possible genetic factors.

The findings were striking: "The suicides clustered in four primary pedigrees, and the role of inheritance was suggested by the way in which suicides followed the distribution of affective disorders in these kinship lines," the researchers say. The majority (92 percent) of the 26 suicides occurred in persons diagnosed with major affective disorders, and they occurred in families with higher incidence of depression, manic depression and other affective disorders. The researchers conclude that appropriate intervention and treatment for these disorders is especially warranted in patients with a positive family history.

By interviewing family members, affective disorders were diagnosed for all but one of the suicide cases: there were 12 bipolar (manic depressive) cases, 12 unipolar (severe depression) disorders, one unspecified psychiatric disorder, and one case of minor depression. Except for the person with minor depression, the families of all suicide victims also showed increased incidence of affective disorders, the researchers note. Every person with bipolar disorder who committed suicide had first-or second-degree relatives with bipolar and unipolar disorders.

Of the 26 suicides, there were 21 men and five women; the mean age for men was 41 years and for women, 55 years. The range for men was 18 to 69 years, with most occurring their prime; the range for women was 42 to 72 years. The majority were married and had children; one woman and four men were single. Only six had received any psychiatric care; the other 20 had either received no treatment, were seeing a family doctor, or were "planning to do something."

JAMA August 16, 1985



Be prepared, Doctor. More patients will be asking about colorectal cancer. According to a survey* conducted by the American Cancer Society, many people would like to receive more information about colorectal cancer, and 83% said they would want to be checked for it. Further, they are learning that this cancer can be detected *before* symptoms appear. The present cure rate is 44%. The cure rate *could* be as high as 75%, with early detection and appropriate management.

For asymptomatic persons the Society recommends annual digital rectal examination at age 40 and over; at age 50 and over, an annual stool blood test, as well as sigmoidoscopy every three to five years,

following two initial annual negative sigmoidoscopies.

We're here to help. You can reach us at your local American Cancer Society office or write to our Professional Education Department at National Headquarters, 90 Park Avenue, New York, N.Y. 10016. Ask about the Society's Colorectal Check program of professional and public education for the early detection of colorectal cancer.



*"Cancer of the Colon and Rectum: Summary of Public Attitude Survey," Ca 33:359-365, 1983 (Nov.-Dec.).

This space contributed as a public service.

Medicolegal Decisions



PATIENT BLIND FROM SALICYLATE POISONING SUES FOR MALPRACTICE

A patient who was permanently blinded by salicylate poisoning was entitled to a new trial of her malpractice claims against a physicians and a hospital, the Alabama Supreme Court ruled.

The patient visited the physician, a specialist in Internal Medicine, in January 1977, complaining that her stomach filled up easily. X-rays revealed the presence of a bezoar, calcified particles and foreign material mixed with food and secretions forming a sausage-like mass. The bezoar was treated with meat tenderizer and subsequent X-rays showed it to have dissipated. In April 1977, her physician advised her to take Ecotrin, an enteric-coated aspirin for her arthritis.

In June 1977, she returned to the physician and complained of mildly acute symptoms similar to those experienced earlier. Suspecting a recurrence of her former condition, the physician had her admitted to the hospital for examination. X-rays confirmed the existence of a bezoar in her stomach and suggested that it was composed in part of undissolved tablets. The next day the patient's condition changed dramatically and she became comatose for about three weeks. When she was discharged from the hospital, her condition was diagnosed as permanent loss of vision. The loss of vision was caused by salicylate poisoning from the Ecotrin tablets in her stomach. The bezoar had apparently broken up and passed into her lower intestine, where the aspirin was absorbed.

She filed a malpractice action against the hospital and treating physician. A trial court directed a verdict in favor of the hospital, and a jury returned a verdict in favor of the physician.

On appeal, the court remanded the case for a new trial against the physician and the hospital on the negligence claims. There was evidence that the hospital radiologist failed to inform the treating physician of X-rays showing a large number of pills in the patient's stomach. That presented a jury question on the issue of whether the hospital had breached its duty to the patient. The trial

court should not have directed a verdict in favor of the hospital.

The court's instruction to the jury that if the patient's injuries were caused by someone over whom the physician had no control, then he was not liable, was erroneous, the court said. The instruction which the court gave did not take into account the well-recognized principle that the physician may be liable for his own negligence even though other people not his agents are also liable for their negligence.—Davison v. Mobile Infirmary, 456 So.2d 14 (Ala. Sup.Ct., July 16, 1984; rehearing denied, Aug. 24, 1984)

SURGEON NOT NEGLIGENT IN PERFORMING LAMINECTOMY

A surgeon did not breach the standard of care in performing a laminectomy, the Alabama Supreme Court ruled.

The 27-year-old patient underwent a laminectomy on May 18, 1979. During the course of the operation his blood pressure dropped, necessitating an emergency procedure to repair the left common iliac artery and vein, which had been lacerated during the laminectomy. The patient filed a malpractice action against the operating physician. A trial court granted summary judgment in favor of the physician, and the patient appealed.

Affirming the decision, the Supreme Court said that the testimony of the patient's expert witness established that the operating physican did not breach the standard of care during the surgery. The court reviewed the expert witness's testimony as a whole and decided that his initial misunderstanding of the legal definition of standard of care had been rectified by the conclusion of his testimony. The expert stated that an occurrence such as the laceration of the blood vessels was a surgical accident and did not equate with negligence. The court concluded that there was not a scintilla of evidence from which a jury could reasonably conclude that the operating physician's acts fell below the required standard of care.

The trial court's grant of summary judgment in favor of the physician on the negligence claim was affirmed.—

Malone v. Daugherty, 453 So.2d 721 (Ala.Sup.Ct., May 4, 1984; rehearing denied, June 22, 1984

AUTO ACCIDENT VICTIM SUES HOSPITAL FOR NEGLIGENCE

A hospital was not entitled to summary judgment in an action against it for negligence in failing to diagnose and

treat a patient's broken jaw, a federal trial court in Virginia ruled.

The patients was admitted to the hospital's emergency room on April 18, 1981, for treatment of head and chest injuries received in an automobile accident. He was comatose when admitted and remained so for eight more days. He alleged in his complaint against the hospital that its medical staff was negligent in not diagnosing or treating a broken jaw that he suffered in the accident. He sought \$200,000 in damages for pain and suffering and the expense of various dental services.

The hospital moved for summary judgment on the ground that the treating physicians were independent contractors, not employees of the hospital, and that the hospital was not liable for their negligence. Denying the hospital's motion, the federal trial court said that the patient's claim was based on the apparent authority of the physicians to act for the hospital. The court said that it was obvious from the filings that there were genuine issues of material fact in dispute concerning the extent to which the hospital held out the treating physicians as its agents.

Virginia case law made it clear that whether the hospital held out the physicians as its agents was a question of fact for the jury to decide, not a matter of law for the court to rule upon. The fact that the patient was in a coma when he was brought to the hospital and remained unconscious for eight days was a factor to consider in determining whether the hospital held out the physicians as its agents to the patient, the trial court ruled.—Walker v. Winchester Memorial Hospital, 585 F.Supp. 1328 (D.C., Va., May 21, 1984)

NEW TRIAL FOR SUIT FOR CARE OF THROMBOPHLEBITIS

A wrongful death judgment against two physicians who treated a patients for deep vein thrombophlebitis should be reversed and remanded for a new trial, an Illinois appellate court ruled.

The patient was injured in a fall on January 23, 1975. For several days afterwards he was treated by an orthopedic surgeon, who diagnosed a sprained wrist and possible sprained and bruised knee. The patient complained of increasingly severe pain in his right calf throughout that period and was eventually admitted to a hospital. There he was treated for deep vein thrombophelbitis. On February 8, 1975, six days after treatment began, the patient died from a massive pulmonary embolism.

In a wrongful death action against the physicians who treated him for thrombophlebitis, his estate argued that they failed to administer the proper amount of herpain and failed to detect symptoms of pulmonary edema and treat condition. A jury returned verdicts in favor of the patient against the two treating physicians, and they appealed.

Reversing the decision, the appellate court said that a new trial was necessary because of erros in jury instructions given by the trial court. The trial court erred in instructing the jury that the drug manufacturers' recommendation on dosing of heparin was a standard against which the physician's conduct was to be measured. It also erred in instructing the jury that it could consider the hospital formulary and a statement of laboratory procedure on administration of heparin to be proof of the standard of care.

The court remanded the case for a new trial.—Young v. Cerniak, 467 N.E.2d 1045 (III.App.Ct., Aug. 3, 1984)

PATIENT SUES PHYSICIAN FOR FAILURE TO DIAGNOSE HIS WRIST FRACTURE

Summary judgment was precluded in a malpractice action where there were substantial factual questions requiring resolution at trial, an Ohio appellate court ruled.

In July 1980, a patient went to a hospital emergency room after he injured his wrist. An attending physician read on X-ray as negative for fracture. The patient was released with his wrist bandaged and in a sling. He was advised to see his own physician for follow-up care. the next day a radiologist also read the X-ray as negative.

Thinking the wrist was only sprained, the patient did not seek follow-up care. Ten months later, in May 1981, the pain in his wrist was worse and the patient returned to the hospital. X-ray of the wrist at that time revealed a fracture, and corrective surgery was necessary.

In May 1982, the patient filed an action for malpractice, alleging that the physicians, as agents of the hospital, were negligent in failing to diagnose the fracture. He presented an affidavit of an expert stating that the first X-ray did reveal a fracture, which was the same as that seen on the first X-ray.

The physicians contended that the action was barred by the statute of limitations. One physician submitted an affidavit of an expert that the fracture in the second X-ray was sustained after the date of the first X-ray and that the care the physician provided the patient satisfied the standards for comparable physicians in these circumstances. The trial court granted summary judgment for the physicians and hospital.

On appeal, the court said that a retrospective date-ofdiscovery rule had been adopted after the trial court's decision, providing that an action for malpractice accrues and the statute of limitations begins to run when a patient discovers or should have discovered an injury. The court said that the rule applied in the present case, and therefore the patient commenced his action within a year afte the cause accrued. The court found that there were issues that precluded summary judgment, including whether there was one fracture, seen on both X-rays, or a later fracture at the same physicial point. Further, if there was only one fracture, there was a question as to whether there was negligence in failing to diagnose it. Reversing the trial court's decision, the court sent the case back for further proceedings.—Obral v. Fairview General Hospital, 468 N.E.2d 141 (Ohio Ct. of App., Nov. 21, 1983)

FAMILY OF PATIENT WHO DIED OF PULMONARY EMBOLISM LOSES MALPRACTICE SUIT

A hospital and a surgeon were not liable on a claim that they failed to warn a patient of the danger of an embolism from a vein-stripping procedure, a Missouri appellate court ruled.

The patient was 5'10" tall, weighed 280 pounds, and suffered from open sores on his feet that made walking painful. His physician diagnosed his problems as arising from varicose veins and recommended a vein-stripping operation. He warned the patient of risks from surgery, including death, but not specifically of the danger of pulmanary embolism, which he regarded as an insignificant risk from vein-stripping surgery.

The patient had been treated in the past for thrombophlebitis. The patient agreed to the surgery and a venogram was taken, which showed that the deep venous system was clear. The patient signed a consent form after reading it, and the surgery was essentially uneventful. The patient left the hospital to return home three days after the surgery. The next morning he died of a massive bilateral pulmonary embolism.

In a wrongful death action against the hospital and the surgeon, a jury returned a verdict in favor of the surgeon on the claim that he failed to warn the patient of the danger of a embolism as a result of the surgery. The trial court directed a verdict in favor of the hospital on the claim that the hospital was negligent in obtaining the patient's consent to surgery.

Affirming the decision, the appellate court said that the hospital had no duty to inform the patient of the risks involved in surgery and possible alternative methods of treatment. That duty rested with the physician. The court said the patient had read and signed the consent form, and the hospital had no additional responsibility to ascertain whether the patient understood it.

The court said that the verdict in favor of the physician was supported by the evidence. The court noted that it was possible that the jury placed more credence in the testimony of the physician with 25 years' experience in vascular surgery than it did in the testimony of the patient's physician-lawyer expert whose only experience with vein-stripping operations occurred no more than five times while he was an intern. The trial court's decision was affirmed.—Ackerman v. Lerwick, 676 S.W.2d 318 (Mo.Ct. of App., Sept. 4, 1984)

NO NEGLIGENCE IN CARE OF PARALYZED ACCIDENT VICTIM

A physician and a hospital were not liable for irreversible spinal cord damage suffered by a patient in or after an accident, a federal appellate court for Alabama ruled.

The patient was injured in an automobile accident. He had been drinking for the previous two days. When the

ambulance arrived, the emergency medical technician strapped the patient into a hard backboard and attempted to sandbag his neck. During transportation to a hospital, the patient struggled to free himself from the straps to the backboard and tried to sit up, despite warnings that any movement could be dangerous. The technician described the patient as uncooperative and noticed that he smelled of alcohol.

In the emergency room, personnel who initially examined him believed he was extremely drunk. Their examination revealed no neurological problems. The emergency room physician was unable to identify the source of the patient's pain in his neck except for an abrasion on the shoulder blade. He was admitted for overnight observation.

At about 10:00 p.m. that evening a nurse noticed that he was exhibiting sings of paralysis. The on-call doctor was summoned and he immobilized the patient's neck and ordered X-rays. He ordered the patient transferred to another medical facility which was better equipped to handle a neurological patient. It was ultimately determined that the patient had fractured two cervical vertebrae. Resultant damage to the spinal cord left the patient a permanent quadriplegic.

The patient filed suit against the emergency room physician and the hospital for negligent diagnosis and treatment. The jury returned a verdict in favor of the physician and hospital, and the patient appealed.

Affirming the decision, the appellate court said that there was sufficient evidence for the jury to find in favor of the physician and hospital. There was medical testimony that regardless of the medical care given to the patient, he could have incurred irreversible spinal cord damage either during the wreck itself, while being assisted to the side of the road or while being transported to the hospital. There was also expert testimony that the patient's own movements could have caused the ultimate injury.

The court concluded that the jury's verdict was based on substantial evidence and should be affirmed.—Haney v. Mizell Memorial Hospital, 744 F.2d 1467 (C.A.11, Ala., Oct. 26, 1984)

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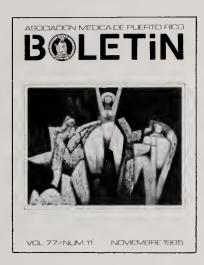
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NUESTRA PORTADA



Luciémaga - Acrílico de Augusto Marín.

Augusto Marín nació en el 1921 en Santurce, Puerto Rico. Cursó sus primeros estudios con el artista español Alejandro Sánchez Felipe. En el 1946 se convierte en director artístico de Publicidad Badillo. De 1950 a 1952 es director artístico de la revista "Temas" de Nueva York y del 1954 al 1957 trabaja como director artístico de la agencia de publicidad Maz Associates. En el 1955 completa sus estudios de dibujo y pintura en el Art Student's League de Nueva York estudiando bajo la tutela de Reginald Marsh, Harry Sternberg, a Ivan Olinsky. Cursa también estudios en Los Angeles County Art Institute de California. Regresa a Publicidad Badillo en el 1958. En el 1964 estudia la técnica del vitral con el maestro Arnaldo Maas siendo becado por el Instituto de Cultura Puertorriqueña para completar sus estudio de vitral en Maastritch, Holanda.

Comienza a enseñar diseño y pintura en la Escuela de Artes Plásticas del Instituto de Cultura Puertorriqueña en el 1966. Desde 1974 es profesor en el Colegio Regional de Carolina y en el 1983 cursa estudios de litografía en la Universidad de Notre Dame en Indiana.

Los seres que pueblan la naturaleza sugieren disafíos a la imaginación artística. Ellos presentan a Augusto Marín un yacimiento de posibilidades que le facultan para agotar los modos figurativos tradicionales e incursionar en la búsqueda de todo tipo de distorsiones válidas. Las formas de vida en su estado original promueven en el pintor interrogantes encadenadas/orientadas a conocer las realidades prevalecientes tras las fachadas. Su máximo deleite reside en el trato con la gente. Por eso dedica gran parte de su esfuerzo artístico a extraer toda posibilidad admisible en la siluetas de sus congéneres. Las bestias llaman su atención y repite en ellas pesquisas similares para obtener resultados equivalentes. Ese procedimiento le da visa para dilatar su expediente de alternativas con el fin de poder rebasar consistentemente sus trabajos. Utiliza ese método como antídoto contra soluciones formulistas que conducen a petrificaciones estilísticas.

Marín ha colocado su enriquecimiento intelectual al servicio de su arte. Periódicamente se registran en su obra evoluciones notables cuyos

atributos responden a situaciones que se nutren del curso existencial del momento. Piensa que el proceso creativo responde a imperativos que surgen como actos de fe. Es posible que el ambiente sacramental que impregna muchos de sus lienzos provenga de la necesidad de manifestar convicciones espirituales. De esta manera, sus efectos visuales surten en el observador resultados a corto y a largo plazo. Para que sus imágenes se graben de manera indeleble en las mentes de los contempladores hace que varios factores intervengan en sus trabajos. De capital importancia es la fuerza que imprime a sus representaciones; ese procedimiento ahuyenta de ellas todo indicio de timidez. Así mismo, estudia cada mensaje a fin de convertir el soporte en parcela natural donde reside su idea. Dar permanencia a sensaciones que deben conservar su vitalidad en superficies inertes provoca tensiones entre autor y medio. El paso que le conduce a hacer sobrevivir la chispa de vida que da origen a la concepción requiere una domesticación de los materiales. Esa potestad del pintor sobre los elementos que utiliza es imprescindible para hacer reinar lo imaginativo.

La obra que aparece en la portada pertenece a la colección del autor. Su reproducción ha sido posible gracias a la gentileza del Sr. Marín y a la cooperación de la Sra. María Rechany de la Galería Rechany en la Calle Navarro de Hato Rey.

Fé de Errata

La obra que aparece en la portada del número de Octubre de 1985, titulada Consultando, pertenece a la colección del Sr. José Luis García. La obra de Rechany sobre el mismo tema titulada La Consulta es la que pertenece al Sr. Luis Ferré.

El editor solicita sea disculpado por los inconvenientes que este error pueda ocasionar.

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EDITORIAL

La Enseñanza de Medicina Interna en el Consorcio Educativo de la Escuela de Medicina de la Universidad de Puerto Rico

C abemos que la educación universitaria en las cien-Cias requiere el uso de laboratorios donde el estudiante aprende, aplica y domina las destrezas y técnicas que acompañan al conocimiento. La enseñanza de la Medicina requiere igualmente el uso de Talleres Clínicos (laboratorios) donde el estudiante aprende a tomar un historial y a hacer un examen físico, a observar la enfermedad en el paciente, a establecer un diagnóstico de presunción, a hacer un diagnóstico diferencial y a trazar un plan de estudios de laboratorio y de manejo del paciente. En escuelas de medicina con currículos de 4 años, la enseñanza de primero y segundo año es principalmente de ciencias básicas. Usualmente, el diagnóstico físico se ofrece en segundo año y la experiencia clínica en los últimos 2 años de estudios. En la Escuela de Medicina de la Universidad de Puerto Rico (EMUPR) aproximadamente el 60% de las horas del programa de estudios se realiza fuera de los salones de clase.

No existe legislación en Puerto Rico creando un Hospital Universitario para la EMUPR. La Ley Núm. 378, del 15 de mayo de 1949, que creó la Escuela de Medicina a la misma vez dispuso: "Por la presente se autoriza y ordena al Secretario de Salud a hacer los arreglos necesarios para el uso del Hospital de Distrito de Bayamón y cualquier otro Hospital, clínica o centro médico u hospitalario bajo su jurisdicción administrativa, en relación con el establecimiento y funcionamiento de la Escuela de Medicina de Puerto Rico".

Del 1952 al 1960, la Escuela utilizó el Hospital Municipal de San Juan en la Parada 20 como su principal taller de enseñanza. En enero de 1960, la Escuela mudó su enseñanza clínica al Hospital de Distrito de Bayamón que había sido relocalizado en el antiguo Hospital Alejandro Ruiz Soler. El nuevo nombre del antiguo hospital pasa a ser el Hospital (Distrito) Universitario.

La EMUPR, para el 1965, tiene como principales hospitales de enseñanza el Hospital Universitario, el Hospital de Veteranos y el Hospital de la Capital localizados en Monacillos en Río Piedràs. En el 1966 comienza a aumentar el número de estudiantes admitidos a la EMUPR lo que suscita la necesidad de tener que

ampliar los talleres clínicos. El Departamento de Medicina de la Escuela comienza en el 1967, en base voluntaria, la oferta de pasantías del internado pre-grado ("junior internship") para estudiantes de cuarto año en el Departamento de Medicina del Hospital Regional de Ponce. Luego lo extiende a Mayagüez. La experiencia acumulada por varios años demostró, fuera de duda, no sólo la deseabilidad, sino la viabilidad de la utilización de hospitales fuera de San Juan como talleres de enseñanza clínica.

En el 1970 se prepara en EMUPR un nuevo programa de estudios para el estudiante de medicina. Este nuevo currículo se redacta a base de objetivos terminales, lo que permite que el estudiante identifique con claridad qué es lo que debe aprender en cada materia y que, además, facilita que la facultad, irrespectivo de dónde ésta esté, sepa lo que debe enseñar y a qué nivel de complejidad. Este currículo comienza en el 1973.

En abril de 1975 la Legislatura de Puerto Rico otorga fondos para el comienzo del Consorcio Educativo utilizando, además de los tres talleres clínicos mencionados, el Hospital Regional de Ponce, el de Caguas y el Centro Médico de Mayagüez. El que estos hospitales tengan programas de residencia en Medicina Interna ya acreditados por el LCME y que exista un grupo de médicos en la facultad a jornada completa facilita la tarea del uso de estos talleres. Todos los facultativos a participar en la docencia de estudiantes son elegibles a un nombramiento académico en la Escuela de Medicina de acuerdo a las normas de esta institución.

Al expandirse la matrícula a 150 estudiantes por clase, en el tercer año, se opta por retener 90 de éstos en San Juan y por asignar 60 (40% de la clase) a llevar a cabo sus pasantías durante todo el año escolar en instituciones localizadas fuera de San Juan; 20 en cada uno de los talleres de Ponce, Caguas y Mayagüez. El currículo de tercer año consiste de 12 semanas en Medicina Interna, 12 en Pediatría, 6 en Obstetricia y Ginecología y 6 en Cirugía. En cada trimestre, en la clase de tercer año, asignada a Medicina Interna, hay 30 estudiantes en San Juan; 12 en el Universitario, 12 en Veteranos y 6 en el

Hospital de la Capital. Al mismo tiempo, en cada trimestre, hay de 6 a 7 estudiantes en Medicina Interna en cada uno de los hospitales de Caguas, Ponce y Mayagüez. Los estudiantes, irrespectivo del hospital donde estén, tienen un currículo idéntico con actividades educativas prácticamente idénticas y son evaluados en una forma uniforme por medio de su trabajo con pacientes (mínimo de 16 pacientes), un examen práctico con un enfermo frente al preceptor y un examen escrito que es idéntico para todos los estudiantes.

El análisis de los resultados obtenidos en las tres áreas de evaluación de los estudiantes llevado a cabo, año por año, desde el curso del 1976-1977 hasta el presente, y trimestre por trimestre, demuestra que el aprendizaje obtenido por los estudiantes en los diferentes talleres educativos es equivalente.

Todos los estudiantes de cuarto año tienen que hacer un internado pregrado de medicina interna con una duración de 4 semanas. Del 19 al 27% de los estudiantes de las clases del 1981 al presente han decidido hacerlo en uno de estos talleres fuera de San Juan. Los resultados de la evaluación han demostrado un aprendizaje equivalente.

En los últimos 5 años, de 117 a 134 estudiantes de cada clase han optado por tomar la Parte II del examen ofrecido por el "National Board on Medical Examiners". Sobre el 90% han aprobado Medicina. Al analizar el resultado de estos exámenes, de acuerdo al sitio de la pasantía durante el tercero y cuarto año, no hay evidencia de diferencia en la ejecutoria estudiantil. Esta evaluación externa nos ayuda a confirmar la consistencia interna en el proceso de enseñanza-aprendizaje en el Consorcio.

Los Jefes de los Departamentos de Medicina de estos hospitales, los coordinadores de la enseñanza de estudiantes en cada departamento de cada hospital, los jefes de residentes y los representantes de estudiantes de cada taller clínico se reúnen cada 6 semanas durante el curso en un hospital diferente en forma rotatoria y se evalúa el trabajo realizado, se identifican problemas de operación y se corrigen sobre la marcha.

La experiencia de casi 10 años ha demostrado que la enseñanza de estudiantes a nivel de tercero y cuarto año en los talleres del Consorcio es equivalente. No habría sido posible para la EMUPR el atender la matrícula actual de 150 estudiantes sin la utilización de estos talleres del Consorcio.

Hoy día sabemos que la operación del Consorcio ha sido exitosa, le ha traído beneficios a Puerto Rico y economías al Gobierno. Sin embargo, han habido situaciones difíciles que vencer y han existido múltiples áreas que aún se mantienen sin la aclaración debida. Areas que requieren la atención incluyen la remuneración del personal médico en los talleres clínicos con responsabilidades docentes, incluyendo los beneficios marginales, las relaciones de autoridad y supervisión entre la Escuela de Medicina y el personal médico local, el mantenimiento de las residencias acreditadas en los diferentes hospitales, los cambios de personal y de filosofía a la luz de variaciones en relaciones contractuales, la erogación de fondos para subsanar limitaciones y atender las nuevas iniciativas que el progreso tecnológico exige y otras. Si el Consorcio ha de subsistir es necesario el diálogo amplio y juicioso entre las autoridades de la Universidad de Puerto

Rico y de la Secretaría de Salud y el análisis cuidadoso de lo que éste representa, que ha sido, que es y que se aspira que sea acompañado de las recomendaciones precisas para despejar las áreas que ameritan atenderse.

Mind Suci Palmine W.

Mario R. García Palmieri, M.D. Profesor Distinguido Jefe del Departamento de Medicina del Hospital Universitario

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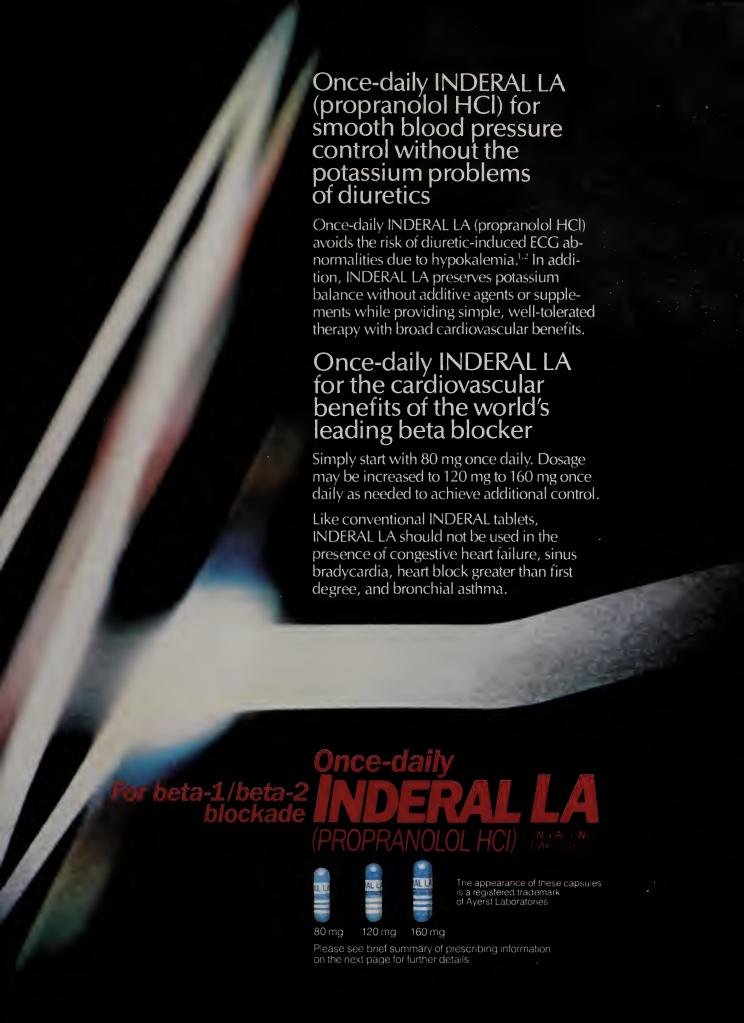
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Right from the start in hypertension...





Once-daily For beta-1/beta-2 NDERAL LA blockade (PROPRANOLOL HCI) LONG ACTING CAPSULES

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
INDERAL* LA brand of propranolol hydrochloride (Long Acting Capsules)
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg. 120 mg, and 160 mg capsules. **CLINICAL PHARMACOLOGY.** INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inofropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCI at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is abouf 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 55% of the AUCs for a comparable divided daily dose in INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect. INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output. (2) inhibition of renin release by the kidneys, and (3) diminution of ionic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic set Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the

been shown to cause a small increase in serum potassium concentration when used in the

been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients. In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

pressule and systolic ejection period. The left physiologic effect of beta-adriently biochaete is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity. In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action in the treatment of arrhythmias is uncertain. The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenetic receptors have been demonstrated in in the pial vessels of the brain. Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm. Progranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the freatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia freatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supwaknings. Cardinal Fallone: Sympathetic stimulation may be a vital component sup-porting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart

muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice fix INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occuli atherosclerotic heart disease who are given proprianoid for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—
PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of bela receptors. MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of

the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthe-sia and surgical procedures



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INDERAL (propranolol HCI), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g. dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

beta blockers
DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin
THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism
Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. General: Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Pafients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a refurn of increased infraocular pressure. Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease,

clinical Laboratory less: Elevated blood urea levels in patients with severe heart disease, elevated serum fransaminase, alkaline phosphatase, lactate dehydrogenase. DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervos activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

hypotension Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was

levels Reproductive studies in animals did not show any impairment of lertility that was attributable to the drug Pregnancy Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman. Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension; paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

tension; paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type

Central Nervous System. lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic, pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm

Hematologic, agranulocytosis, nonthrombocytopenic, purpura, thrombocytopenic.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic

purpura

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been

reported Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL INDERAL LA has different kinerics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval HYPERTENSION—Dosage must be individualized. The usual initial dosage is 80 mg INDERAL LA once daily whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 for 160 mg once daily In some instances a dosage of 84 mg mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks. ANCINA PECTORIS—Dosage must be individualized. Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established. If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

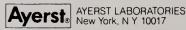
(see WARNINGS)

MIGRAINE—Dosage must be individualized. The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose. INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of

should be discontinued it may be advisable to find the several weeks
HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily
PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too
limited to permit adequate directions for use

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1. Holland OB, Nixon JV, Kuhnert L: Diuretic-induced ventricular ectopic activity. Am J Med 1981;70:762-768. 2. Holme I, Helgeland A, Hjermann I, et al: Treatment of mild hypertension with diuretics. The importance of ECG abnormalities in the Oslo study and in MRFIT. JAMA 1984;251:1298-1299



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ESTUDIOS CLINICOS

Chronic Lymphocytic Leukemia: A Study of 53 Patients and Review of the Literature

G. Martínez-Poventud, M.D. J. Fradera, B.S.M.T. J. Cintrón-López, M.D. E. Vélez-García, M.D., F.A.C.P.

Abstract: Chronic lymphocytic leukemia is a disease known to have a highly variable clinical course. Although it is the commonest type of leukemia in the western hemisphere, only 53 patients with CLL have been seen at the University Hospital during the last 14 years. Most patients were caucasian, with a mean age of 61 years and 3:2.3 male predominance. The initial laboratory evaluation revealed hypogammaglobulinemia in 8 patients and a positive Coomb's test in five. Only one patient had clinical manifestations of hemolysis and no other immune phenomena were observed. The following complications were seen: pathologic fracture, hyperuricemia and a second primary malignant tumor, one patient with each. Clinical staging was performed according to the RAI schema: 0:12(23%), I:11(21%), II:17(32%), JII:5(9%), and IV:8(15%). Most patients required treatment due to lymphadenopathy and splenomegaly. All patients received chlorambucil with or without prednisone. The observed response rate was 66%. All stage IV patients were poor responders with only 1 of 6 having a partial remission. Four deaths occurred during the first 6 months after diagnosis; one in stage III and three in stage IV disease. Twenty two (22) patients have been followed for a minimum of 5 years; of these: 7(31%) died, 3 in stage III and 4 in stage IV disease. Our study suggests that perhaps a more aggressive approach should be tried initially in patients with advanced stages at presentation. In spite of the small number in our series, the results compare favorably with those reported from other major centers.

Chronic lymphocytic leukemia (CLL) is a malignant lymphoproliferative disorder characterized by the gradual accumulation of morphologically mature-appearing lymphocytes in the peripheral blood, bone

marrow, lymph nodes and spleen, eventually involving any organ system. The lymphocytes are usually of B-cell lineage¹ and often are immunologically incompetent. CLL is a disease of the elderly and has a variable clinical course and prognosis with a median survival of 5 years. Since the introduction of a new clinical staging system by Rai et al in 1975, clinical investigation in this disease has prospered² and some of the prognostic factors have been identified.

The purpose of this study was to determine the clinical presentation, course and response to therapy of all the patients with the diagnosis of CLL followed by us at the University Hospital in order to outline the clinical characteristics of this disease in Puerto Rico.

Material and Methods

The records of all adult patients with the diagnosis of CLL seen at the University Hospital in San Juan, Puerto Rico, from August 1970 to February 1985, a 14-1/2 year period, were reviewed.

There were 53 patients who were either diagnosed or followed by one of us in our institution. The variables analyzed were: age and sex, serum gammaglobulin levels, Coomb's test, response to therapy, complications, and survival.

The diagnostic criteria of CLL were based on an absolute peripheral blood lymphocyte count ≥ 15,000/mm³, ≥ 50% bone marrow lymphocytes and < 10% lymphoblasts in blood and bone marrow. All the patients were staged according to the Rai classification,³ and the response to therapy was defined as: complete remission (CR), when all parameters returned to normal; partial response (PR), when all measurable parameters improved 25% or more and non responder (NR), when a status less than PR was obtained. The 5 year survival was determined by evaluating the patients diagnosed prior to February 1980.

Results

Sex and Age

Of the 53 patients in this study 30 (57%) were males and

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23 (43%) females. The male to female ratio was 3:2.3.

The age groups at diagnosis are shown in Figure 1. Ages ranged from 25 to 88 years, 3 (13%) females and 1 (0.03%) male were under age 50. The mean ages were 63 for males and 59 for females, with an overall mean age of 61 years. All the patients were staged according to the Rai classification (Table I).

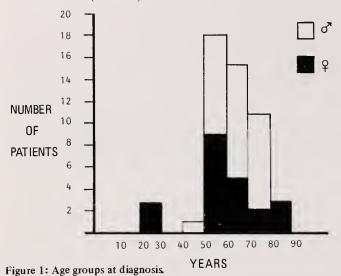


TABLE 1

	Rai Classification									
Stage	Clinical Findings									
0	Lymphocytosis only									
1	Lymphocytosis with enlarged lymph nodes									
11	Lymphocytosis with enlarged spleen and/or liver									
111	Lymphocytosis with anemia									
1V	Lymphocytosis with thrombocytopenia									

The distribution of patients according to prognostic groups is presented in Table 2. Although the numbers are small, there were no significant differences in prognostic groups compared to stage at diagnosis, age and sex. In the high risk group twenty five percent of the patients presented either with stages III or IV at diagnosis.

Serum protein electrophoreses were performed in 39 patients: 8/39 had hypogammaglobulinemia; 11/39 had diffuse hypergammaglobulinemia and the rest (20 patients) had normal patterns. One patient had clinical manifestations of hemolysis and was found to have increased levels of serum IgM (>1000 mg%). No other immune phenomena or episodes of hypersensitivity reactions were observed.

Treatment

Thirty-five patients (66%) required treatment mostly due to symptomatic lymphadenopathy and splenomegaly. All patients received chemotherapy with chlorambucil, with or without prednisone, in an intermittent or daily regimen. Four patients received splenic radiation and symptomatic improvement was achieved in all of them. Two stage I and one stage II patient received total body irradiation (TBI) in addition to chemotherapy.

The response to therapy with chlorambucil by stage distribution is shown in Table 3. There were 7 (20%) CR, 16 (46%) PR and 12 (34%) NR, with an overall response rate of 66%. Five of the non-responders were stage IV patients; two of these were chlorambucil non-responders and achieved CR with the MOPP regimen (nitrogen mustard, vincristine, prednisone, and procarbazine), while the other three were treated unsuccessfully with CVP (cyclophosphamide, vincristine, and prednisone).

TABLE III

Distribution of the Response According to Stage After Therapy with Chlorambucil

	No. of	Responses								
Stage	Patients	CR	PR	NR						
0	4	1	2	I						
1	8	2	5	1						
11	13	4	6	3						
111	4	0	2	2						
1V	6	0	1	5						
otals	35	7	16	12						

TABLE 11

Distribution of Patients According to Prognostic Group

		9	% of Patients b Age Groups	у	No. of Patients (%)					
Prognostic Group	Stage	<50 yr.	50-70 yr.	> 70 yr.	Males	Females	Overall			
Low Risk Intermediate Risk High Risk	0 1 & 11 111 & IV	0 6 2	17 35 17	4 12 6	6(20) 17(57) 7(23)	6(26) 11(48) 6(26)	12(23) 28(53) 13(24)			

Laboratory Findings

Coomb's tests were done in only 20 patients. Only one patient in the series had clinical manifestations of hemolysis and there were 5 positive Coomb's tests out of the 20 tested.

Survival and Complications

Eleven patients were lost to follow up and 20 patients have not yet reached five year follow up after diagnosis. Eleven patients have died during the 14 1/2 years of the study period; all had advanced stages of the disease

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except one stage II patient who died of an acute myocardial infarction 5 years after CLL was diagnosed.

Twenty two (42%) patients were evaluable for 5 year survival analysis, (Table 4). 15/22 (68%) survived at least 5 years; all seven deaths occurred in the high group (stages III and IV); four of these patients died within 6 months of diagnosis (figure 2). Of the 15 five year survivors, 12 lived more than 5 years (9 are still alive at 6+, 6+, 6+, 8+, 9+, 9+, 11+, 13+, and 19+ years after diagnosis), the remaining 3 died after 9 years of follow-up and were all stages III and IV.

The following complications were observed: autoimmune hemolytic anemia (one patient); pathologic fractures (one patient); a second primary malignancy (one patient); five cases of sepsis and one patient with hyperuricemia.

Clinical Staging Distribution of the

TABLE IV

	5 and 10 Ye	ear Survivors							
	No. of	Survivors							
Stage	Patients	5 Years	10 Years						
0	4	4	1						
ĭ	4	4	2						
II	5	5	1						
III	4	1	0						
IV	5	1	0						
Totals	22	15	4						

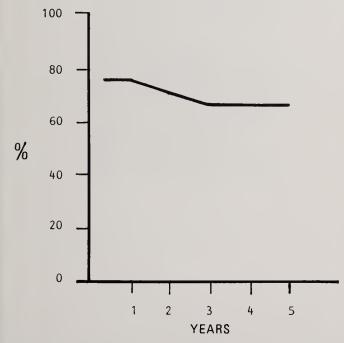


Figure 2: Percent of Patients surviving the first five years after diagnosis.

Discussion

Since the development by Rai et al^{2, 3} of a staging system for CLL, new advances in the characterization of this disease have been made thus leading to better understanding of the clinical and therapeutic approaches as well as to the recognition of a category of high risk

patients. Furthermore, Binet et al⁴ in 1985 proposed another prognostic classification based on a logistic multivariate analysis which was subsequently recommended by an International CLL Workshop as a modification to the Rai staging system in order to avoid confusion and to provide an even more uniform data base which would serve as common ground to all those interested in this disorder.

In the past, many studies were carried out in order to identify prognostic factors in CLL because of its highly variable clinical course, difficulty in establishing the initiation of a therapeutic approach and the slow in vitro growth potential of cell cultures of the malignant lymphoid cells.

In order to have a better understanding of its etiology, many countries have reported on the racial and geographical distribution of CLL patients.⁵ Although a specific pattern of inheritance has not been established, this disease is the most common type of familial leukemia⁶ and has been found more frequently among eastern european descendants and caucasians in the western hemisphere and among Japanese survivors of the atomic catastrophes. It is a disease of the elderly and after the 6th decade, the most common type of leukemia in the United States and Europe. Among caucasians, the median age at diagnosis is 55 years and the male predominance ratio is 2:1 to 3:1. In our series, the mean age at diagnosis was 61 years, slightly older than the expected; and the male predominance (3:2.3) was lower than previously reported. Our female patients were younger than the males and the distribution according to prognostic groups at diagnosis was even for both sexes. Several studies3, 7 have shown that age and sex should no longer be considered reliable prognostic factors since differences in survival rates have not been consistently found.

In CLL, two populations, short-lived and long-lived lymphocytes are overproduced.^{8, 9} The life span of the long-lived lymphocytes is increased to 5 years. Several types of circulating lymphoid cells have been identified, however, the lymphocytes in the vast majority of patients are usually of B-cell lineage and less than 10% of the cases are of T cell origin. The most common cytogenetic abnormality in CLL¹⁰ is an extra chromosome 12 or a translocation to chromosome 14 (14q+).

The diagnostic criteria are based on (1) absolute lymphocyte count above 15,000/mm³ (2) at least 40% lymphocytosis in the bone marrow and (3) less than 10% lymphoblasts in blood and bone marrow. Approximately 1/4 of the patients are asymptomatic at diagnosis and as the disease progresses may develop symptoms related to lymphadenopathy, hepatosplenomegaly, anemia and thrombocytopenia. Systemic infiltration by the neoplastic cells may occur in any organ system, frequently affecting the skin (leukemia cutis) and the kidneys in over 50% of the cases.

The anemia is usually normochromic, normocytic, and the direct Coomb's test is positive in about 20% of the cases. Occasional patients may develop immune throm-bocytopenia, pure red cell aplasia or hypersensitivity syndromes. Hyperuricemia may occur in about 30% of the cases. Only one case was observed in our series, probably as a result of effective preventive therapy with

allopurinol and hydration.

The major complications in CLL are: sepsis, hypercalcemia, symptomatic anemia or thrombocytopenia and second malignancies. The incidence of associated or subsequent second malignancies is around 20%. The most frequent second malignancy seen in association with CLL is skin cancer. 11, 12 Only one instance of a second malignancy was observed in our series in a patient with a previously treated bronchogenic carcinoma.

The median survival in most reported series is 5 years. Zippin¹³ reported a survival rate of only 44% in a large series of 839 patients at 5 years. The introduction by Rai et al of a clinical staging system based on the extent of the disease has permitted the identification of a population of high risk patients. This staging system correlates with survival; the median survival ranges from 11 years for stage 0 to only 1 1/2 years for stage IV patients. In our series actuarial 5-year survival has been achieved by 68% of the patients; a slightly better survival rate than expected. All deaths occurred in stage III and IV patients, the high risk group^{3, 14} due to advanced disease and its complications.

Because of the indolent course of this disorder many patients required no therapy at all although the indications for therapy have not been uniformly standardized. Generally, patients are not treated unless they have: "B-symptoms", painful or rapidly increasing adenopathy or splenomegaly, autoimmune manifestations, or bone marrow failure.¹⁵

Standard initial therapy in CLL is primarily with alkylating agents, particularly with chlorambucil which may be given on a daily or an intermittent schedule as a single agent or with steroids, with a reported response rate of approximately 60%. At the present time studies are in progress to determine if a daily or intermittent chlorambucil regimen with or without total body radiation is more effective in achieving a higher response rate than chlorambucil alone.¹⁶

Complete remissions are rare, but those achieving CR have a more favorable clinical course and prolonged survival.¹⁷ In our series a 66% response rate was achieved; as expected, the poorest response was observed in stage IV patients. Although we have used combination chemotherapy sparingly in CLL, this modality is now also under careful study to evaluate its possible effects on survival. These aggressive therapies should be tried only in the high risk group of patients, in order to curtail potential complications such as second malignancies and secondary leukemias which tend to be high in these circumstances.¹⁸, ¹⁹, ²⁰

In conclusion, our clinical experience in following 53 patients with CLL over a 14 1/2 year period has been summarized. We observed no major differences from other reported series except for possibly the very low incidence of secondary leukemias and other second malignancies in our environment. Median survival, age and stage distribution at presentation as well as response to treatment were similar to those reported from other countries. Newer outlooks should be undertaken to evaluate a more aggressive initial therapeutic approach for patients presenting with advanced stages of the disease.

Resumen: La leucemia crónica linfocítica tiene un curso clínico muy variable. Es el tipo de leucemia más frecuente en el hemisferio occidental, sin embargo, hemos tenido la oportunidad de evaluar y seguir solo 53 pacientes durante los últimos 14 años. La mayoría de los pacientes eran de origen caucásico, con edad promedio de 61 años y predominio en el varón a razón de 3:2.3. Ocho de los pacientes presentaron con hipogamaglobulinemia y cinco con la prueba de Coomb's positiva. Solo un paciente presentó manifestaciones clínicas de bemólisis y no se observaron otras manifestaciones inmunológicas. Entre las complicaciones se informaron: una fractura patológica, una neoplasia secundaria y un paciente con hiperuricemia.

El estadío clínico se llevó a cabo siguiendo el esquema de Rai: 0:12 (23%), I: 11(21%), II: 17(32%), III: 5(9%), y IV: 8(15%). Las indicaciones para tratamiento en la mayoría de los casos fueron la presencia de linfoadenopatías y esplenomegalia. Todos los pacientes recibieron chlorambucil con o sin prednisona y un 66% de éstos obtuvieron respuestas a la quimioterapia. Las peores respuestas se observaron en los pacientes en estadío IV. Cuatro pacientes fallecieron durante los primeros 6 meses después de hecho el diagnóstico, uno en estadío III y tres en estadío IV. Unos 22 pacientes han tenido un seguimiento mínimo por 5 años, de los cuales: 7(31%) fallecieron, 3 en estadío III y 4 en estadío IV. Este estudio sugiere que tal vez, una terapia más agresiva debe ser ofrecida inicialmente a aquellos pacientes que se presentan en estadíos avanzados. A pesar del reducido número de nuestra serie, los resultados comparan favorablemente con los informados por otros autores.

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Hepatocellular Carcinoma in the University Hospital

Estber A. Torres, M.D.* Evelio Bravo-Fernández, M.D.**

In 1982, seventy-five new cases of primary carcinoma of the liver were reported in Puerto Rico, for an adjusted incidence rate of 1.8 per 100,000 persons. Although this incidence has remained stable since 1965, it represents approximately a four-fold increase from the decade of the 1950's.¹ This incidence is still considered low as compared to the rest of the world. Hepatocellular carcinoma has a geographic distribution, showing an incidence of over 20 per 100,000 in Taiwan, Asia and South Africa.² Both chronic Hepatitis B viral infection and pre-existing cirrhosis have been considered as etiologic factors for the development of this malignancy.², ³, ⁴, ७, 8, 9

In order to better define the nature of our patients with heapatocellular carcinoma, we studied the population of the University Hospital with a histologic confirmation of hepatoma from 1962 to 1983.

Materials & Methods

The records of the Cancer Registry of the University Hospital from 1962 to 1963 were reviewed, and all cases with the histologic diagnosis of hepatocellular carcinoma were identified. These files contain information including age, sex, history of previous malignancy, some clinical data, presence of metastasis, survival, cause of death and autopsy findings when performed. All patients in whom the diagnosis of cancer is made are found in this Registry. A total of 78 cases were obtained from this source.

From this list, twenty-five clinical records were obtained from the Puerto Rico Medical Center. These records were reviewed and the following information charted: age, sex, pertinent history, symptoms, signs, laboratory abnormalities, operative or autopsy findings, evidence of metastasis, histology, and treatment.

Results

Of the total of seventy-eight patients, fifty-three were male and twenty-five were female, for a ratio of 2.12:1. Ages ranged from 18 to 93, with a mean of 58.1 in males and 62.1 in female.

Sixteen of the twenty-five patients had history of alcoholism, while only six had a history of hepatitis. One patient had received treatment for Schistosomiasis, and no one had been exposed to drugs or hepatotoxins.

The most frequent presenting symptom was abdominal pain (20 patients), followed by weight loss (17 patients), jaundice (9 patients), and increased abdominal girth (6 patients). Less frequent were upper gastrointestinal bleeding (5), fever (5), anorexia (4), and presence of a

mass detected by the patient (4).

Hepatomegaly was present in 14 cases, ascites and jaundice in 9 each, and a palpable mass in 3.

An increased alkaline phosphatase was present in the twenty-four patients in whom it was tested. Elevation of the SGOT (23/25) and of the LDH (17/21) were also very frequent. Elevation of the serum bilirubin was noted in 17 of 25 cases. Most patients were anemic, with only one showing erythrocytosis. Four of eighteen had hypoglycemia. Serum albumin was frequently below normal (14/20). Only two patients were tested for HBsAg and one of the two had a positive test. Alpha-feto protein was not tested.

Eighteen patients underwent a liver-spleen scan, showing a cold defect in fourteen. Of these, four also had a Gallium Scan performed and three of these were positive for a lesion that concentrated the tracer.

Of the twenty-five histologic specimens, 13 also showed cirrhosis: 11 of the post necrotic or macronodular type, 1 classified as micronodular, and 1 unclassified. Twenty-two of the twenty-five tumors were pure hepatocarcinomas, and three had mixed areas of cholangiocarcinoma.

Although information on metastatic disease was not available in all patients, the majority of those undergoing autopsy had evidence of spread of disease at the time of death. Local extension to the gall bladder and regional nodes, as well as the portal vein and inferior vena cava, lungs, and bones were frequent.

Data on survival was available on 75 of the 78 patients, two were lost to follow up, and one died an unknown date.

The survival is shown in Fig. I. At 6 months 13.3% were alive, and only 8% at one year. Two patients survived beyond 24 months, one dying at 25 months and the other at 11 years 11 months. Both died of their liver cancer.

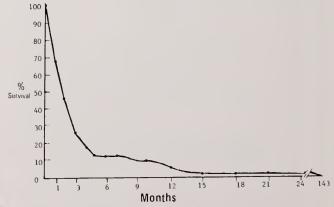


Figure 1. Survival curve in 75 patients with hepatocellular carcinoma in the University Hospital

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A very limited number of patients received some form of therapy. Two patients of the seventy-eight had a hepatectomy, one died within one month and the other survived 11 years 11 months. Twelve received chemotherapy, three survived more than 1 year. Other interesting findings were the development of hemoperitoneum in 2 patients and a perforated duodenal ulcer in 2. One patient had a concomitant adenocarcinoma of prostate, and one patient had been treated for Hodgkin's lymphoma 9 years before.

Discussion

Hepatocellular carcinoma has an incidence that ranges from less than five cases per 100,000 in the United States, which is low, to a very high one of over twenty cases per 100,000 in Taiwan, Japan and some parts of Africa. The incidence in Puerto Rico in 1982 was 1.8 cases per 100,000,1 which falls within the low incidence of the United States. The ratio of male to female in Puerto Rico for 1982 was 1.6:1, and in the University Hospital it was 2.12:1. The general ratio is reported to vary depending on whether cirrhosis is present or not.2

Etiologic factors for this malignancy include chronic hepatitis B virus infection and alcoholic cirrhosis, 2, 7, 9 Other considerations are the presence of liver disease secondary to alpha₁ antitrypsin deficiency, hemochromatosis, exposure to aflatoxins, cytotoxic drugs and anabolic steroids. The last three are mainly speculative, with no clear data to implicate them.2, 9, 10 Schistosoma japonicum was found in 32 of 232 patients with hepatoma,3 but no cause-effect relationship was established. In our series, sixteen patients had history of alcoholism, six had history of hepatitis and one had been treated for Schistosomiasis. Thirteen had cirrhosis proven by histology, of which eleven were postnecrotic or macronodular, one was micronodular and one was unclassified. The coexistence of hepatoma and cirrhosis may be as high as 75 to 80% in the United States4, 5 and 83.5% in Japan. The lower incidence (52%) in our series may reflect underdiagnosis due to biopsy sampling errors, since not all patients had an autopsy performed. The histologic classification of cirrhosis would suggest some role for viral disease, but unfortunately, HBsAg determinations were not readily available in our hospital until recently and were done in only two patients. None of the liver biopsies showed involvement by Schistosomiasis. Martinez et al reviewed twenty-six cases of hepatoma in 1965 and found no cases of Schistosomiasis.6 These findings suggest that Schistosoma mansoni, although a frequent cause of portal hypertension in Puerto Rico, is not a predisposing factor in the development of hepatocellular carcinoma.

The presentation of the tumor in our patients is similar to that found elsewhere, with abdominal pain and palpable mass, jaundice, and ascites,² followed by other symptoms such as anorexia, weight loss, fever and gastrointestinal bleeding. Frequently this presentation is indistinguishable from decompensated cirrhosis.

The most frequent laboratory finding was elevation of the alkaline phosphatase, and metabolic alterations such as hypercalcemia (1 patient), erythrocytosis (1 patient) and hypoglycemia (4 patients) were infrequent. Alphafeto protein has been detected in up to 80-95% of patients with hepatoma,⁵ but this test was not available in our hospital at the time.

The dismal prognosis of this condition may be partly explained by the late diagnosis and presence of metastasis at the time of presentation. Therapy yields poor results with the exception of patients in which limited disease allows a resection of the tumor. Survival is therefore also very poor. In the years 1973 to 1979, one year survival in Puerto Rico was 7% in males and 14% in females. Martinez and co-workers reported a survival of 0 to 48 months, with an average of 7 months. Our one year survival was 8%, and the only patient alive after five years had undergone a resection, in spite of which he eventually died of liver cancer.

We conclude that hepatocellular carcinoma in Puerto Rico has a clinical behavior similar to that in the United States. We have insufficient data regarding the presence of cirrhosis or preexistent Hepatitis B Virus infection to suggest an etiologic factor. Nevertheless, we feel a preventive approach to this condition should include the prevention of hepatitis B, and the control of alcoholism. A close follow up of patients with cirrhosis could lead to early diagnosis and possible beneficial therapy.

Summary: A series of twenty five patients with the histologic diagnosis of bepatocellular carcinoma at the University Hospital is presented. An analysis of pertinent bistory, clinical presentation, laboratory findings, presence of cirrhosis and survival is included.

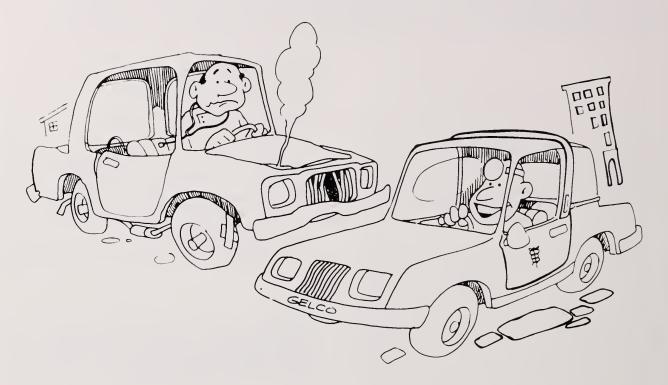
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Peritonitis in Continuous Ambulatory Peritoneal Dialysis: Five Years of Clinical Experience

Francisco Joglar, M.D. Ivet1e Rivera, R.N. Virginia Martínez, M.S.

In September 1977 the University District Hospital Renal Center initiated a Continous Ambulatory Peritoneal Dialysis (C.A.P.D.) program for patients with End Stage Renal Disease. During the first five years of the program 52 patients have been trained and five additional patients have been transfered to the program from other institutions. In this paper we describe our experience with peritonitis during these five years interval.

Methods

The patient's peritoneal access was achieved through a single cuff, permanent Tenckhoff peritoneal catheter to which an extension tubing leading to a peritoneal dialysis solution bag containing either 1.5%, 2.5% or 4.25% dextrose was connected by mean of a screw-type titanium adpater (Baxter-Travenol, Deerfield, Illinois). The patients would perform four exchanges per day and were instructed to use 2.5% or 4.25% dextrose exchanges as necessary to control sodium and water balance.

Thirty seven (65%) of the 57 patients were men; the age range of all patients was from 13 to 76 (median 42) years. The primary diagnosis of the renal disease included chronic glomerulonephritis in 32, diabetes mellitus in 10, nephrosclerosis in six, adult polycystic kidney disease in 4, interstitial nephritis in 2. obstructive uropathy in 2 and hereditary nephritis in one.

Diagnosis and Treatment of Peritonitis

All the patients were instructed to come to the Renal center upon the development of a cloudy dialysate or abdominal pain. As soon as they arrived samples of the dialysate were taken for leukocyte count, gram stain and culture. A dialysate white cell count greater than 100 cells per cubic millimeter, where 50% or more of the cells were polymorphonuclear neutrophil, was consistent with a diagnosis of bacterial peritonitis and treated accordingly. Samples for cultures were obtained by removing 5cc by sterile needle and syringe and after having cleaned the medication port by a five minutes betadine drop from the contaminated dialysis bag which were then injected into a culture bottle and sent to the microbiology laboratory for plate incubation.

Nephrology Section, Department of Medicine, University of Puerto Rico School of Medicine, University of Puerto Rico, School of Public Health and Biostatistics

During the time of observation the therapeutic approach was varied significantly on three occassions. From September 1979 to March 1981 the therapy was initiated by adding cephalotin in a dose of one gram to the first bag; 500mg to the second bag and 250mg to all subsequent bags if the gram stain showed a gram positive or no organism; gentamycin 80mg to the first bag, 40mg to the second bag and 16mg to all subsequent bags if gram negative bacterias were seen and the patient instructed to continue their dialysis technique to conclude 10 days of antibiotic therapy. Those patients which were too ill to continue their CAPD were hospitalized and their exchanges performed by the nursing staff. From March 1981 to May 1984 the initial therapy was varied to start all patients with a combination of cephalotin and tobramycin in the same dosis as described above, mixed together in the same dialysate bag. From May 1984 on, the combination was varied to vancomycin one gram plus gentamycin 80mg in the first bag, vancomycin 40mg plus gentamycin 40mg in the second bag and vancomycin 40mg plus gentamycin 8mg to all subsequent bags. The frequency of the exchanges was increased to every four hours during the first 48 hours of therapy. Once the results of the cultures were available, the antibiotic therapy was then varied accordingly. The patients which persisted with symptoms, a cloudy dialysate or a dialysate white cell count greater than 100 cells per cubic millimeter where 50% or more of the cells were polymorphonuclears after 48 to 72 hours of what was considered to be an appropiate therapy would undergo removal of the peritoneal catheter. Also those patients with an associated subcutaneous tunnel infection and patients with fungal peritonitis would undergo removal of the peritoneal catheter and were transferred for hemodialysis.

Results

There were 83 episodes of peritonitis in 42 patients distributed as follows: 42 first episodes, 23 second episodes, 12 third episodes, 5 fourth episodes and one fifth episode. No peritonitis occurred in 15 patients. The cumulative experience of 843 patients-months yields and overall incidence on one episode every 10.16 patientmonths. Table I shows the peritonitis rates in each of the five years of the study.

Table II shows the number of organisms cultivated by year of study. There was a persistent predominance of gram positive organisms followed in number by gram negative organisms. There was a tendency for higher

TABLE I

Peritonitis	Rate	in	Each	of	the	Five	Years	of	Study

	Months on Treatment	Episode of Peritonitis	Patients Months Per Episode
1979 - 1980	100	16	6.25
1980 - 1981	202	21	9.61
1981 - 1982	165	13	12.69
1982 - 1983	183	11	16.63
1983 - 1984	193	22	8.77

response per year of study is even more self evident consequently, the need to remove a peritoneal catheter due to an infection refractory to therapy has also decreased markedly during the last two years. During the first three years of the study a total of six cathethers per year had to be removed for the above mentioned complication while on the fourth year only three catheters had to be removed and in the fifth year only one.

Of the twenty five patients requiring admission to the hospital six occurred in the first year of the study, 10 in

TABLE II

	Organisms Cultured by Year of Study												
	Gram Positive	Gram Negative	Mix Gram Neg. and Gram Pos.	Fungiis	No Organisms Found								
1979 - 1980	5	3	0	1	7								
1980 - 1981	7	5	0	1	8								
1981 - 1982	5	2	1	0	4								
1982 - 1983	4	3	0	1	4								
1983 - 1984	14	4	1	0	3								

culture yields per year of study with a consequent progressive decline in the number of culture where no organism was found. The overall culture growth experience was: 43% gram positive organisms, 20% gram negative organisms, 4% fungii, 2% mixed gram positive and gram negative organisms and 31% with no growth of organisms.

Table III shows the 83 episodes of peritonitis broken down by episode number, year of the study and by the outcome as to recover versus no recovery from the peritonitis insult. There was a tendency for a higher recovery rate as each year went by; particularly during the last two years of the study (9 out of 11 in year 4 and 21 out of 22 in year 5). If the recovery rate is analyzed for the first episode of peritonitis alone, the progressive increase in

the second year, 6 in the third year, 3 in the fourth year four in the fifth year. Only one death which occurred during the first year of the observation period could be attributed as a consequence of a peritonitis.

The year of inception in CAPD of the fifteen patients without peritonitis were as follows: 4 patients started in 1980; 4 patients started in 1981; 3 patients started in 1982 and 2 patients started in 1983. Further evaluation of these same fifteen patients by sex classification revealed that 13 were male and two were female. Table IV shows that the incidence of peritonitis is significantly less in our male than female population (0.39 with the raw chi square and 0.081 with the corrected chi square). This group of patients was also studied by age group but no pattern of significance was found.

TABLE III

Peritonitis Episode		1		2		3		4		5
Year	R	NR	R	NR	R	NR	R	NR	R	NR
1 1979 - 1980	7	6	3	0	0	0	0	0	0	
2 1980 - 1981	7	2	4	2	4	2	0	0	0	0
3 1981 - 1982	4	1	2	4	0	1	l	0	0	0
4 1982 - 1983	5	1	1	1	2	0	1	0	0	0
5 1983-1984	9	0	6	0	3	0	2	1	1	0
Total	32	10	16	7	9	3	4	1	1	0

R = Recover from peritonitis

NR = No recovery from peritonitis

TABLE IV

	Count Row %	No Peritonitis	With Peritonitis	Row Total
Sex		0.	1	
	1.	13	24	37
Male		35.1	64.9	64.9
	2.	2	18	20
Female		10.0	90.0	35.1
	Column	15	42	57
	Total	26.3	73.7	100.0

Corrected Chi Square = 3.03294 with 1 desree of freedom. Significance = 0.0816

Rew Chi Square = 4.22988 with 1 desree of freddom. Significance = 0.0397

Discussion

Our incidence of one peritonitis episode every 10.16 patients months or 1.18 episodes per patient year is lower than that reported in the National CAPD Registry of the National Institute of Health (January 1984) and which varied between 1.6 and 1.8 episodes per patient year.²

The etiologies of the peritonitis were essentially the same as that reported by other authors³ with the exception of our rather high rate of cultures with no growth of organisms (31%). The tendency of higher culture yields during the latter part of the study period points to an improvement in this respect, even though the explanation for it was not forthcoming.

There was an encouraging increase in the recovery rate from peritonitis, particularly during the last two years of the study (9 out of 11 in year 4 and 21 out 22 in year 5), with a concomitant decrease in the need to remove a peritoneal catheter due to this complication. Of the several reasons which could be cited for this finding the following seem to be of major importance: the employment of antibiotics in combination at the initiation of treatment (cephalosporine and an aminoglycoside or vancomycin and an aminoglycoside) which have been shown to be stable in commercial peritoneal dialysate and will in most cases increase the rapidity of bacterial killing.^{3, 4, 5} The other explanation is that as reported elsewhere,⁶ the learning experience of a given center will bear on the outcome of the patients.

That a small number of patients will remain free of peritonitis is in accordance with previous reports, but the finding that in this group there was a significant predominance of males must await further experience.

Even though peritonitis continues to be a problem in the CAPD, patient improvement in its management through the sharing of documented experience should allow for a significant decrease in the number of dropouts from a CAPD program as a result of this complication.

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A Longitudinal Prospective Study Among Puerto Rican Diabetic Patients

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he principal aim of the University Group Diabetes Program (UGDP) was to study the relation-ship between type of therapy and appearance of diabetic complications. There was an implicit aim to study the degree of correlation between tight metabolic control (IVAR, or insulin variable) and not-so rigid type of therapy (PLBO, or placebo groups). The latter took diet and pills made to resemble either tolbutamide (TOLB) or phenformin (PHEN). The unexpected appearance of a higher cardiovascular mortality among the TOLB and PHEN-treated UGDP groups brought such therapy to a halt. At the conclusion of the UGDP study, no clear-cut results had emerged in regards to type of metabolic control and long-term complications.² Indeed, it was at the time of closing the study that one would have expected emergence of a higher or significant number of complications attributable to microangiopathy, such as retinopathy and nephropathy, as well as those related to alterations in the polyol pathway and myoinositol metabolism, retinopathy and neuropathy, which appear 13 or more years after overt diabetes.⁴

Because of the unique set up of Puerto Rico as a small island, and the high degree of dependence and excellent rapport of our patients towards our institution, we decided to continue caring for these patients in the standardized fashion we did during the UGDP study, in a modified way. One of the aims in our study was to assess whether the prevalence of silent myocardial infarctions was indeed higher among such population of non-insulin dependent diabetics, and whether vectorcardiography (VCG) could aid in identifying any such non-fatal events. The latter appeared particularly important, in so far as the UGDP study in general had met with an apparent contradiction, in not having shown a higher rate of non-fatal cardiovascular events, in spite of the higher prevalence of fatal events1 especially among patients receiving oral hypoglycemics agents. This has been interpreted as meaning that severity of such occurrences is higher among diabetic patients with twice as high a mortality rate.5 Alternatively, other means of diagnosing such occurences might yield more information.

In fact, it has been claimed that VCG's could show instances where there were no EKG findings of coronary

artery disease.⁶ Although susceptible to other interpretations, certain investigators have claimed a correlation between such VCG findings as "loop bites" and postmorten evidence of myocardial damage.⁷

With this in mind, we selected for study a sub-group of our UGDP patients who, in addition to their baseline EKG's had also had ramdom VCG's taken.* They comprised 34 patients, and represent about 50% of those we continued to follow up, after the official closure of UGDP protocol. They were re-submitted to VCG's after a mean time of 14 years since diagnosis and baseline characteristics, and an average of 5 years since finishing the UGDP study. Also, findings indicative of long-term complications and their relation to over-all degree of control have been examined in order to study any pertinent correlation between type of initial therapy and subsequent development of complications.

Our data suggests that among this group of patient, there is a correlation between age, mean long-term blood glucose and the extent of micro and (or) macroangio-pathic complications. However, the rate of silent infarcts appears to be small and VCG's do not seem to contribute in diagnosing non-fatal cardiovascular events.

It must be emphasized that in view of the relatively small group number and the arbitrary way of selection (availability of baseline VCG's), these findings could not, and should not be, extrapolated to the complete UGDP study.

Materials and Methods:

Thirty four non-insulin dependent diabetic patients (23 females, 11 males), ranging from 46 to 80 years (mean age: 61 years), were selected for study. These patients had been diagnosed within the year of their inclusion into the UGDP study, having fulfilled the criterion of being able to stay free of ketonuria during a one month observation period. After the close-out of the UGDP study in 1973, these patients continued their follow up at our Endocrinology Section Clinic. Baseline ECG's and VCG's were available for all of them. ECG's were repated annually unless symptoms appeared before the assigned dates. Vectorcardiograms were repeated for comparison with baseline (BL) or entry VCG's. Both the ECG's and VCG's were interpreted by one of the authors (PIA) unaware of other clinical characteristics.

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Quarterly physician examination that emphasized detection of other complications of diabetes, such as neuropathy, peripherovascular disease and retinopathy, were conducted for each year of observation.

The 3 hour OGTT were performed utilizing a test dose of 60 Gm/m² of surface area. The diagnosis of diabetes was made if the sum of 0, 1, 2 and 3 hour whole blood glucose reached or exceeded 500 mg./dl. Fasting blood glucose levels were determined at each quarterly visit by autoanalyzer. Baseline (1963-64) triglyceride and cholesterol values were compared to values obtained in 1978. The upper limits of normal for TG is 150 mg/dl⁸ and that for cholesterol, 250 mg/dl.⁹

A detailed history of recognized risk factors for coronary artery disease (CAD) such as smoking, obesity and arterial hypertension was taken in all patients. A positive history for smoking meant having smoked cigarettes habitually at any time in their life. Obesity was defined as an increase in body weight 20% above the ideal body weight for heights as given by 1959 Metropolitan Life Insurance Tables. Hypertension meant 3 or more determinations during which blood pressure was 160 systolic and 95 mm Hg diastolic or above, while off diuretics or other antihypertensive therapy.

The presence or absence of the following complications have been particularly studied: (1) retinopathy (2) nephropathy (3) neuropathy. The means for diagnosing these have been, respectively, conventional fundoscopic examinations and retinal photography; urinalysis and creatine clearances, and clinical testing for vibration and position sense of the extremities. Our patients' retinopathy was confined to background findings.

All of our patients were switched to IVAR treatment or diet alone either at the time of ending TOLB-PHEN therapy (1969-70), or after closing time of UGDP study

averaged all the fasting blood glucose determination while on UGDP protocol, and have compared these values with mean fasting blood glucose after the termination of the protocol, therefore, while on IVAR or diet alone.*

Results

A. Cardiovascular events (ECG-VCG changes)

1. Initially abnormal ECG-VCG (16 patients). Sixteen, or 46% of the total number of patients, had both an abnormal baseline ECG and VCG. These comprised 12 females and 4 males. Their age ranged from 46 to 80 years (mean: 62.6 ± 9 sem) in 1978. Among these there was only one who changed the ECG-VCG pattern: from that of eqully inscribed ST-T loop to a pattern of myocardial infarction. This patient also developed clinical symptoms of CAD. In this group of 16 patients, 10 (62.5%) had arterial hypertension, 8 (50%) were obese and 3 (18.7%) were cigarrette smokers. Among all patients (n=34), there was only one instance of "silent" myocardial infaction (2.3%) and it showed both by ECG and VCG.

2. Initially normal to abnormal ECG-VCG (5 patients). Table I depicts the clinical, biochemical and ECG-VCG data on this small group of patients. The abnormalities encountered in 1978 were: round loops in 3, Wide QRS in 2 and equally inscribed loops in 2. At the same time the ECG's showed non-specific ST-T wave changes in 4 and an old myocardial infarction in one. Four of these patients (80%) were female, hypertensive and had increased triglycerides. The mean age for the whole group was 60.6 ± 3.7 sem; 2/5 were smokers and 1/5 was obese.

TABLE 1. CLINICAL, BIOCHEMICAL AND EKG-VCG DATA OF PATIENTS WHO CHANGED FROM NORMAL TO AN ABNORMAL VCG

Subject	Sex	Age	♣ B.P.	Smoking	♣ T.G.	♣Chol.	Obesity	Pre FASTING GLUCO		Pre TYPE THE	Post OF RAPY	EKG findings	VCG findings
CEC	ř	52	+	-	+	+	+	198	271	Phen	Ivar	ST-T	Round Loops Wide QRS
PFS	F	66	+	-	+	-	+	129	129	Ivar	īvar	ST-T	Equally inscribed loops (EIL)
LPP	F	66	+	-	+	-	+	162	181	Phen	Ivar	ST-T	Wide QRS EIL
нмн	F	68	+	+	+	+	-	173	158	Plbo	Ivar	old M.I.	Round loops
MAI	М	51	-	+	-	-	-	141	150	Plbo	Ivar	ST-T	Round loops
Totals Means & % positive	4F 80%	60.6 <u>+</u> 3.7	4 80%	2 40%	4 80%	2 40%	3 60%	161 <u></u> 12	178 + 25	2 Phen 2 Plbo 1 Ivar	5 Ivar	4 DT-T 1 o MI	3 Round loops 2 wide QRS 2 EIL

Key & definition of parameters: \phiBP = >160/95 mm Hg; \phiT.G = triglycerides >150 mg/dL; \phiChol = cholesterol > 250 mg/dL; \quad Obesity = over 20\pi ideal body weight. Therapies: Phen= phenformin; Plbo = placebo; Ivar = insulin variable

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3. Normal ECG-VCG (13 patients). The remaining 13 patients maintained normal ECG-VCG's throughout the study. Their mean age was 57 ± 7.1 seem years (range: 46-72). There were 10 females and 3 males. Hypertension was present in 8/13 (62%); 10/13 (77%) were smokers and 9/13 (695) were obese. None of these variables were significantly different intergroups 1, 2 and 3.

B. Mean longitudinal blood glucose

Figure 1 depicts the mean fasting blood glucose while patients were on the protocol compared to the fasting blood glucose values during the subsequent 5 years of follow up, while on IVAR or diet alone. It will be noted that, on the average, these patients achieved better control while on UGDP protocol: 132 ± 1.8 sem vs. $175 \pm 3.7 \text{ mg/dl}$, p < 0.05. This is somewhat striking, for the diet-only patients had rather low mean FBS (Table III) and all other patients were on insulin as required to try achieving the best possible glucose control. It is clear that there was no improvement in control by switching all other patients to IVAR after termination of the UGDP protocol. As their relative body weights were practically unchanged, obesity could not account for seemingly insulin resistance. It is relevant keeping in mind, however that these patients were over a decade older during the last part of the study.

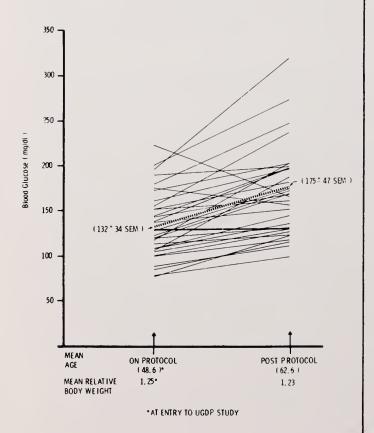


Figure 1: Mean fasting blood glucose while and off protocol

Relation of mean blood glucose to presence of complications:

In the interest of trying to correlate degree of metabolic control (as judged by mean FBG values), to the presence of long term complications, these have been displayed independently in relation to FBG values in Fig. 2. The left-hand values for each correspond to the period while on UGDP Protocol, and the right-side values to the IVAR or diet only on the last 5 years of the study. As each complication is independently depicted, more than total number of patient is displayed.

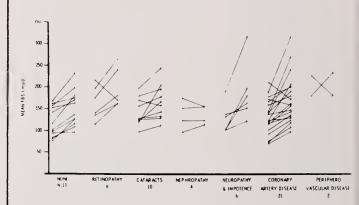


Figure 2: Presence of chronic complications in relation to mean fasting blood sugar while on and off protocol

It will be noted that the most severely uncontrolled patient (mean FBG 319 mg/dl) had neuropathy. Table II gives the detailed features of the 21 patients having some complication, along with their biochemical and EKG-VCG profiles. Table III displays the same information for the group of 13 patients not having any discernible complication. The post UGDP protocol therapy for patients in Table II is not given as they were all on IVAR. The salient features of Tables II and III have been summarized in Table IV.

It is evident that the mean age among the complicated (C) group is almost a decade higher that the uncomplicated (UC) group. The difference is statistically significant (p < 0.01). Similarly, the mean FBG of the C group while on UGDP protocol (147 \pm 33) was significantly higher than the mean FBG of the UC group (118 \pm 32, p < 0.05). This also applied to the post-UGDP protocol study period, where the corresponding values were $180 \pm 49 \text{ vs.}$ $149 \pm 39 \text{ respectively, p} < 0.05$. Smoking history was present in 52% of C group patient vs. 31% of the UC group patients, but this did not reach statistical significance (p = 0.2). Baseline ECG findings were present to a lesser extent among C patients (38%) than among UC patients (53.8%), but this also failed to achieve statistical significance (p = 0.4). Hypertension, strangely, correlated negatively with the presence of complications, but this, as well as triglyceride, cholesterol, relative body weight, sex and % of EKG-VCG findings were not statistically different.

Table 2. CLINICAL, BIOCHEMICAL AND EKG-VCG FINDINGS AMONG PATIENTS WITH CHRONIC COMPLICATIONS

Subject	Age	Sex	₽ ВР	Smoking	% IBW	С			CAT			∱TG	♣Ghol.	GLU Pre	Post	BL Rx	EKG fi P re	ndings Post	VCG fi Pre	indings Post
WCR	69	М	-	+	+10	-	+	-	-	-	_	+	-	123	168	Tolb	N	N	N	N
L V C	66	F	+	-	+37	-	+	-	-	-	+	+	-	219	165	Tolb	ST	o MI	EIL	a MI
JFC	80	F	+	-	- 5	+	-	-	-	+	-	-	-	127	127	Ivar	i MI	LAD	ifMI	LAD
RMB	63	М	-	-	+16	-	+	-	-	-	-	-	-	146	186	Phen	i MI	i MI	i'MI	i MI
PLR	58	М	-	+	+20	-	-	+	-	-	-	-	+	139	197	Plbo	N	N	N	N
CEC	52	F	+	-	+43	-	+	-	-	-	~	+	+	198	271	Phen	N	ST-T	N	Rd loo
PFS	66	F	+	-	+28	+	-	-	-	-	-	+	-	129	129	Istd	N	ST-T	N	EIL
CVA	55	F	+	+	+38	-	+	-	-	-	+	+	+	179	243	Phen	ST-T	ST-T	Rd L	Rd L
LPP	66	F	+	-	+34	+	-	-	-	-	-	+	-	162	181	Phen	N	ST-T	N	EIL
нмн	68	F	+	+	+10	+	-	-	-	+	-	+	+	173	158	Plbo	N	o MI	Rd L	Rd L
JRM	74	М	+	+	+ 3	+	-	-	-	+	-	-	-	100	117	Ivar	N	N	N	N
NCS	59	М	-	+	+49	-	-	+	-	-	-	-	-	105	188	Tolb	N	N	N	N
JGR	60	М	+	+	- 3	-	-	-	-	+	-	-	-	152	158	Phen	N	N	N	N
BGN	62	F	+	-	+29	+	-	-	-	-	-	+	+	180	198	Phen	iRBBB	iRBBB	iRBBB	iRBBB
AMC	73	F	-	+	+ 5	+	-	-	-	-	-	+	-	127	143	Tolb	ST-T	ST-T	EIL	EIL
JRR	76	М	-	+	+24	-	+	-	+	-	-	_	-	143	167	Istd	N	N	N	N
DSL	6 9	М	-	+	+20	-	-	-	+	-	-	+	-	107	128	Istd	N	N	N	N
FPO	66	F	-	-	+16	+	-	-	-	-	-	+	+	120	205	Phen	ST-T	ST-T	EIL	EIL
CSL	68	F	-	+	+35	-	-	-	+	-	-	+	-	142	157	Phen	N	N	N	N
ASA	54	F	+	-	+43	-	-	-	+	-	-	+	-	191	319	Phen	ST-T	ST-T	Rd. L	Rd. L
RDO	80	F	+	-	+45	+	-	-	-	-	-	+	+	127	172	Ivar	LAH	RBBB	LAH	EIL
ALS & means	66 +8	13F 62%	12 57%	11 52%	·13 ⁶	0 (424)	(318)0	(25\$)∾	(19%) ₽	(19\$) ₽	(10\$) €	14 67%	7 33%	147 <u>+</u> 7.1	180 +10.8	9 Phen 4 Tolb 3 Istd 3 Ivar	2 MI	8 N T 7 STT 3 MI B 1 LAD	11 N 3 EIL 3 RdL 2 MI	

Key for abbvreviations as in Table 1. For complicactions: R=retinopathy;
C= cataracts; I-impotence; n= neuropathy; N-nephropathy; P=peripheral vascular disease. For VCG: Rd L= round loops; EIL=equally inscribed loops
LAH- left anterior hemiblock. For %IBW (#) corresponds to those over 20% IBW.

TABLE 3. BIOCHEMICAL AND CLINICAL PROFILE OF PATIENTS WITHOUT CHRONIC COMPLICATIONS

	Age	Sex	НВР	Hx Smoking	Weight	Mean Pre	FBS Post	TGS	СНО	Rx Pre	Post	ECG BL	1978	BL VC	G 1978
MRV	59	F	_	-	+ 7%	77	99	1	N	Istd	Ivar	CRBBB	CRBBB	CRBBB	N
ALR	61	F	+	+	+ 21%	129	165	N	4	Pbo	Diet	N	N	N	N
CPG	65	М	_	+	+ 24%	121	163	4	*	Pbo	Diet		N	N	N
J4V.A	62	М	+	-	+ 28%	95	117	1	4	Phen	Diet	CRBBB	CRBBB	CRBBB	CRBBB
IBS	46	F	_	+	+ 77%	107	140	^	^	Tolb	Diet	ST-T	ST-T	?	Round Loop
TJC	57	F	+	-	+ 15%	161	236	1	N	Tolb	Ivar	N	N	N	N
LRA	50	F	+	_	+ 56%	154	180	4	N	Phen	Ivar	N	N	N	N
CBR	51	F	+	-	+ 11%	171	201	1	^	Pbo	Ivar	ST-T	ST-T	Eg I	Eq I loop
SRR	57	F	+	-	+ 8%	82	109	N	N	Pbo	Diet	IRBBB	IRBBB	IRBBB	IRBBB
VOB	52	F	+	-	+ 15%	118	132	1	N	Pbo	Ivar	ST-T	ST-T	Eq I loop	Eq I loop
RJM	72	F	+	-	- 2%	103	128	N	N	Phen	Ivar	N	N	N	N
MAI	51	М		+	+ 10%	141	150	N	N	Phen	Ivar	N	N	N	N
BSR	57	F	+	-	+ 27%	76	121	N	N	Pbo	Diet	ST- T	N	Eq I Loop	Eq I Loop

Mean +SD

69%

+23% +21

118 149 62% <u>+8.9</u> <u>+10.9</u> +

Abbreviations as in Table 1.

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TABLE 4. SUMMARY OF CLINICAL, BIOCHEMICAL AND EKG-VCG FINDINGS AMONG DIABETIC PATIENTS HAVING AND NOT HAVING CHRONIC COMPLICATIONS

	COMPLICATED	UNCOMPLICATED	p Value
No. Patients at risk	21	13	
Age (<u>+</u> 1 SD)	66 ± 8	57 ± 7	≺ 0.01
Female Sex	13 (62%)	10 (77%)	NS
♠B.P. (➤160/95 mm Hg)	12/21 (57%)	9/13 (69%)	NS
Hx smoking	11 (52%)	4 (31%)	NS
Obesity (➤20% IBW)	13 (62%)	6 (46%)	NS
TGS (>150 mg/dL)	14 (67%)	8 (62%)	NS
Chol. (>250 mg/dL)	7 (33%)	5 (38%)	NS
BL fasting blood glucose (± 1 SD)	147 ± 33	118 <u>+</u> 32	<0.05
(VAR blood glucose (± 1 SD)	180 <u>+</u> 49	149 ± 39	<0.05
BL EKG findings	8 (38%)	7 (53.8%)	NS
IVAR EKG findings	13 (62%)	7 (53.8%)	NS
BL VCG findings	10 (47.6%)	6 (46%)	NS
VAR VCG findings	13 (62%)	8 (61.5%)	NS

BL = baseline, at entry; IVAR = insulin variable therapy; NS = not significant 1 SD = one standard deviation

Discussion

Atherosclerosis is the leading cause of death among diabetics nowadays.¹¹, ¹², ¹³ Mortality due to acute myocardial infarctions, is high and the rate increases in cases of silent myocardial infarctions, which are more common among diabetics.¹¹ Atherosclerotic lesions in diabetic patients occur more often than in the normal population, develop earlier, and are generally more severe.¹⁴ It is still unresolved whether metabolic control of glycemia can aid in preventing or decreasing the frequency of such events.

Faerman¹⁵ studied autonomic nerve fibers of heart muscle in five patient with painless myocardial infarction and found lesions of diabetic neuropathy in all, while among control patients, i.e., diabetics with painful myocardial infarction (MI), diabetics without MI and non-diabetics without MI, no such lesions were found. This lends support to the belief that painless myocardial infarctions are probably associated to diabetic neuropathy. Mortality resulting from painless MI (40%) is higher than that for symptomatic MI among nondiabetic patients (10-20%).15 Mortality among diabetics with painless MI is presumably increased because MI is not initially suspected and patients are denied of early intensive care. Among 17,654 cases followed at the Joslin Clinic for more than 30 years 11 cardiac deaths accounted for over 50% of the mortality. The incidence and intensity of pain in diabetics with MI was less than in non diabetics. Forty-two percent of diabetics may present with painless MI.¹⁶

In our present study only one event of clinically silent MI occurred, yielding a lower incidence than that previously reported, but without the benefit of anatomopathological correlation.

Based on pathological specimens, Selvester demonstrated that ECG's in diabetics failed to diagnosed MI in 72% of large infarctions and 94% of medium-sized one.¹⁷ He proposed that "bites" seen in VCG tracings were indices of myocardial scars. By his criteria, he proposed that 94% of adult onset diabetics had infarctions. In our group of diabetics, ECG's were as good as VCG for the diagnosis of MI. We found no instance of vectorcardiographic "bites". There was, however, a rather high incidence of VCG changes compatible with repolarization defects which could be secondary to coronary heart disease. These changes may well represent morphologic alterations in the microarterial system, as described 18 by Factor et al, who observed saccular aneurysms of the arterioles and capillary aneurysms of the myocardium on three of the six diabetic subjects studied. However, they were unable to correlate these aneurysms with specific myocardial lesions.

Our results in regards to role of blood glucose control in the prevalence of long-term complications tend to be conciliatory: over-all, we did obtain a correlation between increased blood glucose and prevalence of long-term complications, but individually, there are cases in whom good evidence exists to the contrary. They could constitute a "dilution" factor of the over-all patient population of the UGDP, that could account for the higher-than-expected life span noted among UGDP

patients. On the other hand, such "dilution" would further support the increased risk that such patients sustained during oral hypoglycemic therapy.

The lack of correlation of such cardiovascular risk factors as serum cholesterol, hypertension, obesity and smoking is not without precedent, as similar findings were encountered in the Framingham Study, 19 which led these investigators to conclude that the role of diabetes as cardiovascular risk factor did not derive from an altered ability to contend with known risk factors.

In our present study, the appearance of complications such as retinopathy and neuropathy without preceding hyperglycemia could be interpreted in the light of recent data on genetic pre-diabetics.²⁰ As judged by quadriceps femori muscle biopsies, the capillary basement membrane thickness of 30 offsprings of maturity-onset diabetics was in average 243 Å wider than in normal controls. In that study, both the fixation method (osmic acid instead of glutaraldehyde) and the morphometric technic (average thickness vs. minimum tickness) have been reported to introduce artefactual increase in CBMT,²¹ although another study minimized the role of specific measurement method.²² Those authors concluded that in subjects highly predisposed to diabetes, changes may occur in the microvessels before hyperglycemia, but that hyperglycemia, perhaps acting on a prematurely aging tissue, then becomes an aggravating or precipitating factor.

Some investigators argue that the elevated blood sugar levels found with increasing age is not indicative of a trend toward developing diabetes. They state that higher blood sugar levels should be considered "normal" with advanced age²³ but elevation of blood glucose with increasing decade has been found to be of the order of 2.4 mg/dL only. The insulin receptor is apparently altered as a function of age, as increasing amounts of insulin are needed to achieve the same hormonal effects, atributable to an increase in non-specific binding.²⁴

In the Whitehall study, in which 15,419 men were followed for several years it was found that blood glucose values above 140 mg/dL correlated with a doubling in the relative risk of coronary heart disease mortality, even when corrected for other risk factors:²⁵ In the Framingham study, a negative effect on cardiovascular function was also demonstrated by an impairement of carbohydrate tolerance.¹⁸

There is evidence that argues in favor of the concept that diabetes is a form of accelerated aging:²⁶ In a study done at Case Western Reserve University it was found that collagen fibers from the central tendon of the diaphragm of diabetic subjects were stiffer and more stabilized, just like in aging. In normals, it is possible to estimate with precision the exact chronological age by examining collagen fibers but in diabetics examination of collagen yields ages which are 51 to 65 years older than chronological age. The diabetic subjects, however, did not exhibit accelerated aging in other organs or tissues.²⁷ Collagen is an intrinsic part of vessel walls and the resulting stiffening may be therefore related to cardiovascular disease.

Another form of accelerated aging is shown in the study of replicative lifespan of fibroblasts. It was found

that the life span of fibroblasts obtained for the children of diabetic parents was statistically significantly shorter than those from controls.²⁸

In our study the individual contribution of both factors, i.e., hyperglycemia and aging, could not be distinguished as they coexisted in the study groups.

This is undoubtedly due to the way patients were incorporated into the study in this latter phase, which depended mostly on their availability and the fact that they had vectorcardiograms done originally. The latter was intended as a supplementary study and the taking of VCG's did not imply any specific or non-random bias. Moreover, as no effort was done in preseleting other parameters, results can be due to the "luck of the draw" and, could not be viewed to contain undue biassess working towards the final findings. It would have been of course much better if both the "complicated" and "uncomplicated" groups had been age matched and all cohorts available for follow up.

It could be argued that patients that remained with excellent blood glucose control throughout our study were not diabetics in the first instance. Therefore, oral glucose tolerance curves were repeated in 1980 in these patients and all of them showed diabetic curves.

In order to ascertain better blood glucose control it would have been desirable to measure Hb A₁C or GHb levels in these patients. Unfortunately this method was not available to us at the time of our study, and non existent at the outset of the UGDP.

For obvious reasons the results of this study should not be extrapolated to the complete UGDP study nor to the whole diabetic population.

However, as previously mentioned, these results provide some insight as to the complexities of clinical trials, which contain a heterogenous population and illustrate the need for careful and in depth analysis of such studies before conclusions are safely reached.

Summary: Thirty four non-insulin dependent diabetic were prospectively followed up for a total average period of 14 years, ending in 1978. Among this group we assessed the prevalence of coronary artery disease (CAD), and looked into a possible correlation with degree of blood glucose (BG) control and other known coronary risk factors. The prevalence of silent myocardial infarction (MI) was investigated clinically and through comparison of baseline and 1978 ECG's and VCG's. Presence of other chronic complications of diabetes was also studied.

Twenty one patients (62%), had clinical and/or ECG-VCG abnormalities compatible with CAD. In 16/21 (76%), abnormal ECGs and VCGs remained unchanged; 5/21 (24%) had initially normal ECGs-VCGs. Only one instance of silent MI was encountered and showed both by ECG and VCG. Next most frequent complications were cataracts (9/34, 26%) and background retinopathy 6/34, 18%.

Thirteen patients (38%) had no demonstrable complication. As compared with the complicated group, these had statistically significant lower mean age (57 \pm 6 vs. 66 \pm 8 yrs., p<0.01), and lower baseline BG (118 \pm 32 vs.

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 147 ± 33 mg/dl, p 0.05). No statistically significant difference were found intergroup as to sex, serum cholesterol, triglycerides or relative body weight. Smoking and hypertension were oddly, negatively correlated with such complications. Although higher blood glucose appeared to correlate with prevalence of chronic complications, concomittant higher mean age obscured its role.

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14-060

The Restrictive Pattern of Pulmonary Dysfunction in Bronchiectasis

Ernest L. Cunningham, M.D. Modesto González, M.D. Rafael J. Rodríguez Servera, M.D.

Abstract: Pulmonary function studies of 69 patients with bronchiectasis were reviewed. Cases were divided into "low", "normal" and "high" samples on the basis of residual volume (RV) results of less than 80%, between 80% and 120%, and more than 120% of predicted, respectively. The sample sizes were 23, 30 and 16 cases. These subsamples were found to differ significantly from each other on the basis of other pulmonary function tests as well. The low sample showed a characteristic restrictive pattern, while the high sample showed an obstructive one.

Generally bronchiectasis has been considered a specialized form of bronchitis, and therefore a disease which manifests typical obstructive dysfunction when there is an alteration in pulmonary function in such cases. Most cases of clinically diagnosed bronchiectasis have little functional impairment, or perhaps a slight decrease in vital capacity (VC). In more severe cases the commonest impairment is a decrease in forced expiratory volume (FEV), with a further decrease in flow rates as clinical deterioration progresses.², ³

We have noticed on occasion that patients with bronchiectasis may manifest pulmonary functions which are more compatible with a restrictive process than with that of an obstructive disease. Since this pattern is at variance with what we have noted in the literature, we reviewed the results of pulmonary function studies of patients who have been referred to our laboratory with the clinical diagnosis of bronchiectasis, to see whether any consistent patterns could be found.

Methods

The sample, studied retrospectively, consisted of adult patients who had been referred to the Pulmonary Function Laboratory of the Puerto Rico Medical Center for complete pulmonary function studies between the years 1978 and 1984. The records of all cases which had presented during this time with the diagnosis of bronchiectasis were reviewed. The diagnosis was based on the interpretation of clinical findings by the physician referring each case, and did not imply that any particular diagnostic study or specific set of diagnostic criteria had been satisfied. It was considered that a characteristic clinical picture, as related by the referring physician, was sufficient.

All records of patients presenting with a diagnosis of bronchiectasis during the years under consideration were reviewed. From these cases, those with a previous history of thoractomy were eliminated. Also the records of two women who were pregnant at the time of their studies were discarded. Any patient who had a diagnosis of asthma, as well as bronchiectasis, was also eliminated. Beyond these criteria, no cases were included which did not contain complete and valid findings at least for static lung volume, so that a diagnosis of restrictive pattern could be made if it were present. In those cases where data was present for more than one visit to the laboratory, only the data of the most recent visit was included. Following these exclusions the records of 69 patients were left, so these patients became the sample of this study.

All pulmonary function studies were performed on a Pulmonizer 1525 computerized spirometer from Med Science Electronics. This was connected to a 4051 computer and 4631 hard copy unit from Tektronix. Those tests included in this report are static volume studies, consisting of total lung capacity (TLC), vital capacity (VC), functional residual capacity (FRC), and residual volume (RV); flow rate studies, consisting of the forced expiratory volume in one second (FEV1.0) and the percentage of the forced vital capacity expelled in one second (FEV1%); and studies of diffusion capacity as measured by the steady state technique (DLcoSS).

Standardization of all reports was achieved by comparing measured values to predicted values, and calculating the percentage of variance. Formulas for the predicted values, using sex, age, height and body weight were taken from the program of the Med Science computerized spirometer used for the studies. These formulas are presented in Table I. FEV1% was considered normal if it was above 70 for all subjects. For most age groups the predicted value for TLC was the sum of those for VC and for RV. For certain age groups the predicted values for the DLcoSS were not available.

Statistical significance was determined through use of the Student's T test, taken from formula 548 of the scientific tables edited by Diem and Lentner.⁴

Results

General characteristics of the sample of 69 patients are as follows- 43 patients, or 62.3% of the sample, were females. The average age was 49.5 years, with a range from 15 to 80 years. Average values for all the measured volumes were generally within the normal range, but large standard deviations testify to wide variations in results between individuals. The average values for flow rates and DLcoSS were slightly below the normal range, but again with large standard deviations.

TABLE I

		TABLE I							
	Formulas for Predicted Values								
		Age group: males, ages 6-17.							
	TLC	0.124*exp (0.0216*height) ¹ , ² , ³							
	VC	10 ^ (0.00904*height-0.87567) ⁴							
	FRC	0.056*exp (0.0226*height)							
	RV	0.0358*exp (0.0206*height)							
	FEV1.0	10 ^ (0.00867*height-0.89776)							
		Age group: males, ages 18-24.							
	TLC	VC+RV							
	VC	Height*0.05+age*0.078-5.508							
	FRC	0.1295*height in in5.19							
	RV	0.0687*height in in.+0.017*3.447							
	FEV1.0	Height*0.046+age*0.045-4.808							
	DLcoSS	0.18*height in in0.2795*age+18.37							
Age group: males, age 25 or more.									
	TLC	0.094*height-0.015*age-9.167							
	VC	0.148*height in in0.025*age-4.241							
	FRC	0.081*height-1.792*body surface area-7.11							
	RV	0.0687*height in in.+0.017*age-3.447							
	FEV1.0	0.092*height in in0032*age-1.26							
	DLcoSS	0.18*height in in0.2795*age+18.37							
		Age group: females, age 18-19.							
	TLC	VC+RV							
	VC	Height*0.033+age*0.092-3.469							
	FRC	0.122*height in in5.01							
	RV	0.0813*height in in.+0.009*age-3.9							
	FEV1.0	Height*0.027+age*0.085-2.703							
		Age group: females, age 20 or more.							
	TLC	0.079*height-0.008*age-7.49							
	VC	0.115*height in in0.024*age-2.852							
	FRC	0.53*height-0.017*weight-4.74 ⁵							
	RV	0.032*height+0.009*age-3.9							
	FEV1.0	0.089*height in in0.025*age-1.932							
	DLcoSS	0.172*height in in0.2509*age+15.988							

¹ The symbol * stands for multiplication.

In order to study more closely the relationships between obstructive and restrictive patterns, the sample was divided into three subsamples on the basis of the results for RV. RV was considered the best variable to use as a single determinant of functional pattern, in that it is usually decreased and never increased in purely restrictive dysfunction, whereas it is usually increased in the presence of large airway obstruction. None of the other volumes varies so consistently. Thirty, or 43.5% of the cases, had an RV between 80% and 120% of predicted, so this subsample was considered the normal one, or the control. Table II shows the data for this subsample. Twenty-three, or 33.3% of the cases, had RV less than 80% of predicted, and were considered the low sample. Data for this group is presented in Table III. The remaining 16, or 23.2% of the cases, had RV greater than 120% of predicted, and so were considered the high sample. Data for the high sample is shown in Table IV.

Females comprised 60% of those with normal RV results, 56.5% of those with low RV results, and 75.0% of those with low RV results, and 75.0% of those with high RV results. In the latter subsample females comprise a higher percentage than in the other subsamples. The average age of the normal subsample is 52.3 years, slightly higher than for the other subsamples or for the entire sample. The average age for the subsample with los RV results was 47 years, while that for the high RV subsample was 47.7 years.

The average results of pulmonary function studies for the normal subsample are essentially identical to those of the sample as a whole. For the subsample with a low RV, the TLC is also slightly decreased as are the FEV1.0 and the DLcoSS, but the FEV1% is within normal limits. For the subsample with an elevated RV the TLC is within normal limits, whereas the flow rates are decreased to a much greater extent than for the other subsamples. The DLcoSS, as in the other subsamples, is slightly decreased.

The statistical results of the analysis are summarized in Table V. The subsamples with low and high RV results were each compared to one with normal RV results, and to each other to see if the differences were significant. As would be expected, the differences between the RV values of each of the groups were highly significant, since that is the variable by which the groups were selected. For the TLC values there was a significant difference between the low sample and both the normal and high samples, but the difference between the high and normal samples was insignificant. For FEV1%, the results were just the opposite, in that there was a significant difference between the high sample and both the normal and low samples, but the difference between the low and normal samples was insignificant. For both FEV1.0 and DLcoSS, differences between all samples were insignicant.

These three subsamples form three groups which are significantly different from each other. The smallest is 23 percent of the entire samples, so all are of consequential size. The subsample with low RV results manifests a decrease in lung volumes such as TLC, while flow rates such as FEV1% are preserved. That with high RV results, on the other hand, manifests a disproportionately high RV and a significantly decreased FEV1%.

² The letters exp stand for "raise to a power".

³ Height is in centimeters unless otherwise specified.

The symbol A stands for exponential.

⁵ Weight is in pounds unless othewise specified.

TABLE II

Sample With Normal RV										
#	sex	age	RV	RVpct	TLC	TLCpct	FEV1.0	FEV1%	DLco	DLcopc
I	f	35	1.54	1.04	4.99	1.00	2.37	.69	18.10	1.01
2	f	35	1.47	.97	4.44	.88	1.96			
3	f	38	1.28	1.15	3.70	.93	1.51	.65	11.60	.71
4	f	41	1.18	.97	2.51	.61	.74	.67	7.70	.49
5	f	48	1.55	1.09	3.09	.71	.91	. 59	11.70	.82
6	f	49	1.50	.82	4.28	.81	2.22	.83	12.70	.85
7	f	50	1.46	.96	2.97	.66	.97	.62	9.80	.70
8	f	52	1.17	.84	2.28	.55	1.19	.78	8.90	.68
9	f	55	1.25	1.07	3.24	.93	1.45	.85 -		
10	f	56	1.91	1.09	5.10	1.05	2.13	.65		
11	f	59	1.26	.98	3.52	.98	1.31		8.50	.77
12	f	61	1.40	.97	3.95	1.01				
13	f	63	1.47	1.15	2.89	.84	.60	.72	9.30	.94
14	f	69	1.63	.95	3.50	.82	1.24	.73	8.90	.96
15	f	69	1.62	1.07	4.22	1.11	1.70	.66	7.70	.87
16	f	70	1.71	.97	3.43	.79	1.25	.78	10.20	1.12
17	f	73	1.31	.88	2.36	.66	.60	.33	3.10	.40
18	f	73	1.58	.87	3.02	.69	.96	.69	6.10	.73
19	m	15	1.66	1.14	6.05	.85	3.20	.72	27.70	
20	m	24	.92	.86	3.60	.71	2.31	.87	14.10	.63
21	m	32	1.60	1.12	4.93	.86			4.10	.20
22	m	36	1.86	.97	5.99	.85	1.76	.42		
23	m	39	1.54	.86	3.16	.49	2.50	.69		
24	m	41	1.72	.90	3.99	.60	2.91	.81	13.20	.69
25	m	51	1.85	.87	4,21	.62	2.24	.53	18.80	1.14
26	m	55	1.34	.86	4.51	.96	1.50	.57	15.80	1.16
27	m	65	1.95	.98	5,42	1.00	1.80	.72	5.20	.45
28	m	66	1.98	.98	5.91	1.07	.63	.48	9.80	.86
29	m	73	2.34	1.04	6.30	1.09	1.11	.54	7.70	.80
30	m	76	2.32	1.03	6.05	1.08	2.44	.61	11	1.27

TABLE III

Sample With Low RV										
#	sex	age	RV	RVpct	TLC	TLCpct	FEV1.0	FEV1%	DLco	DLcopct
I	f	23	.86	.71	3.84	.81	1.94	.70		
2	f	24	.62	.47	3.21	.65	1.26		14.90	.73
3	f	27	1.11	.78	4.70	.92				
4	f	28	.77	.53	3.24	.63	1.64	.68	10.80	.55
5	f	31	.80	.56	3.95	.79	2.46	.78	11	.58
6	f	32	.91	.75	3.16	.71	1.75			
7	f	40	1.15	.76	3.32	.68	1.52	.71		
8	f	43	.68	.54	1.60	.39	.40		5.50	.36
9	f	46	1.36	.79	4.49	.87	2.15	.67	8.90	.57
10	f	49	.96	.65	2.82	.64	1.59	.91	6.60	.47
11	f	53	1.39	.77	4.54	.89	2.32	.76	16	1.16
12	f	57	.90	.67	2.05	.54	.55		5.20	.44
13	f	67	1.24	.79	2.43	.61	.60	.54	3.30	.35
14	m	26	1.22	.80	4.67	.73	1.75	.63	17.40	.76
15	m	38	.81	.53	4.15	.73	2.60	.83	16.30	.85
16	m	54	1.17	.72	4.18	.83	1.20		4	.28
17	m	55	1.65	.78	4.37	.68	2.45	.66	15.80	1.05
18	m	59	1.20	.53	5.63	.84	3.35	.73	8.70	.61
19	m	60	1.48	.78	3.61	.66	.78	.49	8.80	.68
20	m	62	1.61	.78	3.89	.66	2.27	.73		
21	m	64	1.57	.72	4.42	.72	1.48	.62	13.20	1.07
22	m	66	1.38	.60	6.53	1.02	2.07	.74	20.40	1.69
23	m	77	.95	.47	2.47	.51	1.23	.82	6.20	.80

TABLE IV

Sample With High RV										
#	sex	age	RV	RVpct	TLC	TLCpct	FEV1.0	FEV1%	DLco	DLcopct
1	f	18	1.45	1.22	3.53	.79	1.11	.49	6.60	
2	f	23	2.10	1.24	4.73	.80	1.70	.61	8.70	.40
3	f	24	1.42	1.31	3.06	.70	1.18	.82	6.90	.34
4	f	33	1.58	1.38	3.13	.74	.85		7.60	.43
5	f	36	1.66	1.39	2.65	.63	.50	.46	5.80	.34
6	f	52	1.79	1.31	4.17	1.03	1.64	.70	10.50	.80
7	f	59	2.76	1.58	4.49	.95	.83	.50	12.80	1.06
8	f	63	2.30	1.59	3.59	.93	.59	.51	16.90	1.64
9	f	68	2.48	1.69	3.96	1.07	.87	.56	17.20	1.91
10	f	69	1.83	1.20	2.68	.70	.51	.61	3.50	.40
11	f	71	1.54	1.33	3.74	1.31	1.39	.57	7.30	.97
12	f	80	2.13	1.46	3.30	1.01	.69	.64	5.10	.89
13	m	16	1.80	1.63	3.08	.57	3.60		9.30	
14	m	35	1.86	1.39	4.02	.76	.88	.37	8.20	.42
15	m	53	2.30	1.31	2.79	.51	1.62	.42	7	.47
16	m	64	2.53	1.40	5.33	1.08	.85		7.50	.66

TABLE V

Statistical Significances Between Subsamples								
Parameters	RVpct	TLCpct	FEV1pct	FEV1%	DLcopc			
Normal n	30	30	28	26	23			
Normal avg	.98	.84	.65	. 66	.79			
Normal s.d.	.10	.18	.21	.13	.26			
High n	16	16	16	13	14			
High avg	1.40	.85	.52	.56	.77			
High s.d.	.15	.22	.28	.12	.50			
sig H:N	.00	.45	.10	.05	.45			
Low n	23	23	22	16	20			
Low avg	.67	.72	.62	.71	.72			
Low s.d.	.12	.14	.23	.10	,35			
sig L:N	.00	.01	.30	.15	.25			
sig L:H	.00	.03	.15	.00	.40			

Notes

sig H:N means significant difference between the high and normal subsamples.

sig L:N means significant difference between the low normal subsamples.

sig L:N means significant difference between the low and high subsamples.

pct as part of the heading of each column means percent of the predicted value.

Significances in boldface are significant to the .05 level of less.

Discussion

We have found three distinct groups among our patients with bronchiectasis. The largest group has pulmonary functions which vary very little from normal, suggesting minimal functional impairment in the presence of significant clinical disease. This is consistent with the findings of others.^{1, 5}

Among the rest of our patients, however, we have found two distinct groups. The smaller one shows decreased flow rates and some degree of air trapping, the classical hallmarks of a pattern of large airway obstruction, which is to be expected in these patients.³ The larger group, however, shows a proportionate decrease in static

volumes and normal flow rates, the classical hallmarks of restrictive disease.

Bronchiectasis is a disease of the airways, usually affecting the larger airways.^{6, 7} For this reason a pattern of large airway obstruction would be the expected functional impairment to be manifested in advancing disease. However, when the destruction which characterizes the morphology of this disease becomes more advanced, significant amounts of parenchyma become involved as well as bronchial tissue.⁷ In a study of airway dynamics in bronchiectasis, it has been shown that, in cystic and varicose bronchiectasis, though not in the cylindrical type, parenchymal tissue beyond the involved large airways is either damaged or filled with liquid

secretions or both, so that intrabronchial pressures are high but insufficient flow can be achieved from the parenchyma to permit an effective cough, and the secretions are therefore retained. Perhaps the increased involvement of the parenchyma in the process of tissue damage, and its decreased involvement in the process of ventilation, could result in the pattern of restrictive dysfunction which is found in a third of our patients. Unfortunately, as we have neither radiologic nor roent-genologic information available for our patients, we cannot identify either the type of bronchiectasis present in each case nor the degree of parenchymal damage. We are only able to identify a distinctive pattern of dysfuction.

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REVIEW ARTICLES

Doppler, M-Mode and Two-Dimensional Echocardiography in Patent Ductus Arteriosus

Charles D. Johnson, M.D., F.A.C.C.

oppler, M-mode and two-dimensional echocardiography have proven extremely useful and important in the evaluation and management of the critically ill newborn and infant who may have a patent ductus arteriosus (PDA), acute pulmonary disease or the combination of these two states, inducing an emergency situation. These diagnostic methods have also proven invaluable in adult congenital heart disease, including the diagnosis and evaluation of PDA.

Case 1

This premature infant presented with respiratory distress, an S₃ gallop and an intermittent heart murmur. Serial two-dimensional and Doppler echocardiographic studies (Honeywell, Biosound. Indianapolis Ind) were performed. The baby was diagnosed as having a PDA; therefore, indomethacin was administered. The ductus arteriousus (DA) closed subsequently and the pulmonary-systemic (Qp/Qs) blood flow ratio normalized.

Figure 1 is a two-dimensional freeze-frame suprasternal notch (SSN) long-axis view of the ascending aorta (AAo), aortic arch and descending aorta (DAo) with the Doppler sample volume (SV) placed in the DAo near the

8 cm

Figure 1

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PDA. A 3.5 MHz angulated transducer was used. Time markers appear at the top and bottom margins of the frame (between the heavy lines represents 1 second, S). An electrocardiogram appears above the image. On the left side of the frame is an A-mode echogram with ramp and gain, and a depth calibration sacale in cm.

Figure 2 is a pulsed-wave Doppler (PWD) flow tracing of the PDA flow from the SSN transducer position. A flow velocity (V) scale is located along the right margin of the freeze-frame; each horizontal mark indicates 10 cm/S. The SV was placed in the DAo near the DA, at 3 cm depth. Positive (toward the transducer) diastolic turbulent (almost continuous) flow and negative (away from transducer) continuous, rough turbulence (less at end-diastole) with slight aliasing are present. These reflect flow both toward and away from the transducer throughout the cardiac cycle indicating a lack of directional flow orientation.

Computer (Apple II Plus-Cupertino, CA; Software disk program-Biodata. Davis, CA) computations and digitizations revealed a Qp/Qs ratio near 2:1; tricuspid flow was used as Qs and Ao flow as Qp.

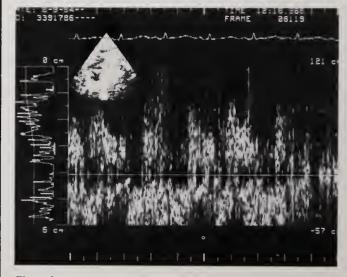


Figure 2

Case 2

Figure 3 is from a newborn with the clinical diagnosis of PDA, and is a two-dimensional freeze-frame image (Honeywell) from the parasternal short-axis view of the right ventricular outflow tract (RVOT), main pulmonary artery (MPA) and the area of the PDA connecting the PA with the DAo below. The left atrium (LA) is located below the central circle of the Ao.

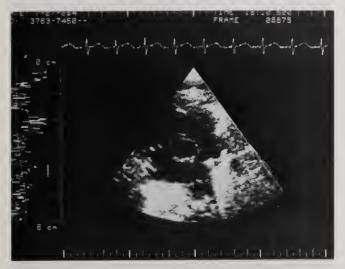


Figure 3

Figure 4 is a PWD flow tracing, with the SV located in the MPA at a 2.5-3 cm depth near parallel to flow, from a parasternal short-axis view (left upper insert). The large PDA can be visualized directly between the PA and DAo. The systolic negative flow represents pulmonary forward flow (peak V 70 cm/S) away from the transducer. The holodiastolic positive, turbulent flow (with decrescendo velocities) reflects ductal flow toward the transducer; peak flow V 90 cm/S. Note valve sounds.

An apical 4-chamber view provided tricuspid flow for calculation of the left-to-right shunt magnitude. The RV appeared large.

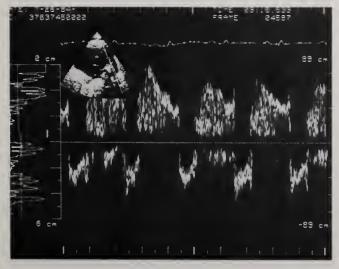


Figure 4

Case 3

This 26-year-old Mexican male suffered electrocution burns. Subsequently, he developed pneumonia, Staphylococcus sepsis, pleural effusion, a pericardial friction rub, scalp and ankle wounds. Surrendipitously, a continuous murmur was heard at the upper left sternal border. An electrocardiogram showed left ventricular (LV) hypertrophy, and an echocardiogram a pericardial effusion. A PDA and/or pulmonic regurgitation (PR) or Ao regurgitation (AR) were considered. Two-dimensional, M-mode and Doppler echocardiograms were repeatedly performed (Honeywell).

Figure 5 is a M-mode frame from the two-dimensional echo (see cursor in left upper insert parasternal short-axis view of the PA and pulmonic valve (PV). A depth calibration scale is present on both sides of the frame. Both anterior and posterior leaflets of the PV are well-visualized. A systolic notch is seen, compatible with pulmonary hypertension (PH), as well as the small "a" wave. Posteriorly is the atriopulmonary sulcus containing the left main coronary artery, behind which is the LA. Most posteriorly is the DAo. There may be a pleural effusion.

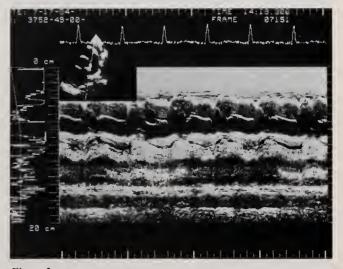


Figure 5

Figure 6 is a parasternal short-axis still-frame view of the RVOT, the PV, the MPA wrapping around the central Ao and bifurcating into the right and left (heavy horizontal white bar) PAs; the left PA continues as the PDA into the DAo below. The MPA dimension measures 2.95 cm, which is large. The Ao is the circle in the left center of the frame; the orifice of the left main coronary artery is seen at its left aspect.

Figure 7 is a short-axis view with PWD. The SV is located in the MPA parallel to blood flow at 9-10 cm depth. The negative systolic flow away from the transducer represents pulmonary forward flow; there is deceleration instability of the curve. Its peak V was 1.3 M/S and mean V 46 cm/S. The time-to-peak velocities (TPV) or acceleration time was 50 mS, indicating PH. Holodiastolic positive flow through the DA toward the transducer indicates a left-to-right shunting PDA.

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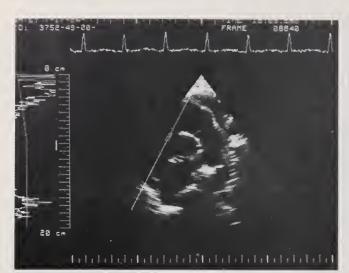


Figure 6

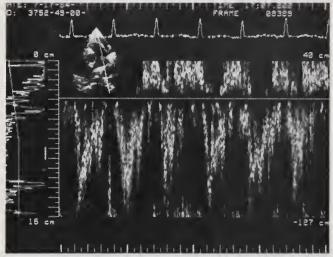


Figure 7

Figure 8 is a parasternal short-axis view with PWD, and a MPA flow trace obtained at a later date when the patien had improved clinically. The SV was located in the MPA parallel to flow at 8 cm depth. Valve opening and closing sounds. Although measurements here may mean little, the diastolic rough flow has a peak V over 50 cm/S and the pulmonary forward flow 1 M/S, showing marked spectral dispersion.

In figure 9 the SV is located in the MPA at 8 cm depth. PWD. The negative holodiastolic turbulent, rough flow present only on this freeze-frame reflects flow away from the transducer into the distal PAs.

In figure 10 the scanhead is in the subcostal short-axis position, and the SV is located in the RVOT just beneath the PV at a depth of 14 cm. The negative systolic trace represents forward flow. The positive diastolic flow toward the probe may be interpreted as PR rather than a reflection of the PDA. It diminishes in late diastole but regurgitant flow persists throughout diastole.

Cardiac catheterization confirmed a large PDA, with an oxygen saturation step-up of 13-14% at the PA level. The PA pressure was 70/50, mean 65 mm Hg, and the

wedge pressure was 23 mm Hg. Ao pressure was 100/60, mean 75 mm Hg. Unfortunately, PR was not specifically evaluated at the time of catheterization. AR was not found.

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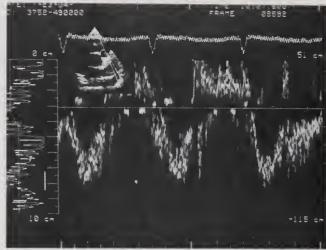


Figure 8

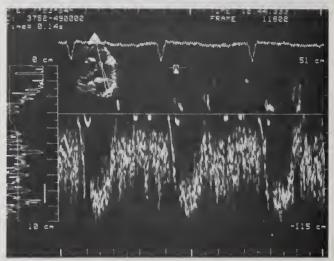


Figure 9

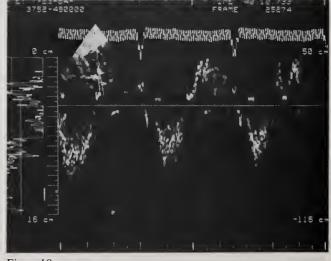


Figure 10

Discussion

The PA and PDA may be imaged from the left parasternal short-axis, the SSN and the subcostal views. Echocardiography in PDA may reveal:

M-Mode

- 1. An increase in LA and LV dimensions; if severe, the end-diastolic dimension is increased as LV volume overload. The septal and posterior wall motion may be exaggerated, and LV contractile indices may be augmented. The RV is normal. Various studies and values on the increased LA/Ao ratio (1.15-1.4) and LA size (5-9 mm or 13.5 mm in various size infants, and over 0.5 cm/M^2 or 2.4 cm in children) have been published in infants with PDA and significant left-toright shunts. The M-mode LA/Ao ratio, LA size and data offer only semiquantitative information which is indirect, limited and with overlap. It is insufficiently sensitive or may mislead. An adult LA dimension over 2.2 cm/M² or over 4 cm indicates enlargement. The SSN view (superior-inferior plane) may reveal LA enlargement not present on the precordial anteroposterior axis. The LV/Ao ratio was 2.10 in premature infants. The LV preejection period/LV ejection time ratio was 0.27 (without heart impairment). After ductal closure or ligation, these values, and the atrial and Ao wall motion, may revert toward normal within hours.
- 2. Unilateral compression or "pancaking" of the LA can occur. Frequently an echo is observed in the LA cavity from the LA promontory which may be mistaken for the LA wall.
- 3. Ao root dilatation, and coarse diastolic fluttering of the mitral leaflets have been observe.
- 4. Serial bedside contrast echocardiography in the neonate via an umbilical artery catheter placed high in the DAo, detected by M-mode or two-dimensional display from the SSN position: a positive study for PDA shows contrast within both the transverse Ao and the right PA; a negative study shows contrast only in the former. A parasternal short-axis twodimensional echo view may show contrast passing in either direction through the imaged DA. Right-toleft shunting in PDA may be evaluated by contrast; a negative contrast effect may manifest in the periaortic area. Two-dimensional echo contrast studies (arterial and peripheral venous) for left-toright and right-to-left shunting are of great value. Contrast studies are needed because clinical evaluation and conventional M-mode do not provide an acceptable diagnostic means. Contrast can identify communications that may be too small to image even with high resolution real-time scanning. Other cardiac lesions can be excluded.

Two-Dimensional Echocardiogram

The DA may be imaged directly from the high left parasternal short-axis, SSN and subcostal views, with the transducer angled more superiorly, for contour and size, as a distal posterior echo-free, curving continuation of

the MPA or left PA junction, connecting to and becoming confluent with the DA (Ao isthmus area). Generally, the ductus of a premature infant is wide and short, but the small ductus of an older infant or young child may be longer or more tortuous and not lying in a single plane and may or may not be visible in its entirety. But different views and good lateral resolution may be necessary to show its variable position and orientation. Serial evaluation of chamber sizes and LV function may be performed. There may be LV dilatation and thickening, a normal or small RV, increased LV fractional shortening, an anteriorly displaced ventricular septum and augmented excursion of the septum and mitral valve. Twodimensional echocardiography in PDA offers very high sensitivity and specificity. Sahn's method was stated to lead to foreshortening of the DA and incomplete visualization along its whole lenght. SSN and left subclavian views were considered superior, safest and most accurate, even in preterm infants, allowing visualization of the aortic arch, distal DA, the main and left PAs, and ductal patency as small as 2 mm.

Doppler Echocardiography

In PDA with lower PA than Ao pressure, blood flows from the Ao to the PA (left to right) during systole and diastole (continuous). The PWD SV is placed into the MPA and bifurcation with two-dimensional guidance, beyond the PV (no valvular clicks should be heard) from the left parasternal short-axis position; Alignment with the RVOT plane is sought, with the transducer angled superiorly, and the patient in the left lateral position. The beam angle should be near parallel (less than 20°) with the blood flow. Normally, with the SV in the MPA, only laminar negative systolic flow away from the transducer into the PAs is present, and diastole is quiescent. A PDA with left-to-right, Ao to PA flow (normal PA pressure), using CWD and PWD from a high left parasternal shortaxis position (or SSN) with the SV in the PA, manifests continuous, positive anterior, high velocity, turbulent retrograde ductal flow toward the transducer. There is marked diastolic or continuous, spectral dispersion with high velocities, which may reach a maximal V of 4 M/S or more, usually maximum at end-systole, falling during diastole and rising again at end-systole. Aliasing may occur throughtout the cycle when the SV is near the DA. The normal negative systolic flow velocity into the PA may diminish the positive systolic PDA signal. The location of the SV in the PA affects the flow patterns. Recently, diastolic negative flow away from the transducer has been appreciated, with certain lateral locations of the SV, while medial locations produce flow toward the transducer during diastole. Systolic and diastolic flutter of the PV can be recorded at times. The systolic and diastolic flow patterns in PDA demonstrate the expected graphics of the classic murmur.

PWD or CWD plus high resolution two-dimensional echo are highly sensitive in detecting ductal patency, when sampling the pulmonary end of the DA: whereas two-dimensional echo can detect ductal morphology it is limited in respect to detection of ductal patency. The aortic and pulmonary ends of the DA can be visualized. Video, still-frames and audio signals are provided.

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SSN Doppler

With a left-to-right shunt, placing the SV initially in the DAo below the PDA may reveal turbulent systolic and diastolic flow (toward the transducer), or nearly normal flow, away in systole or briefly upstream toward the PDA in diastole. This is reversed diastolic flow away from the transducer. The SV is then moved superiorly and rightward to the PDA region, by sweeping the transducer posteriorly, with a leftward twist, or using CWD and low gain, from a left subclavian, long-axis Ao arch view, leftward angulation may reveal the ductal flow. With the SV at the junction of the left PA and Ao or in the PA (the normal systolic negative flow is phasic and smooth), there is turbulent flow both toward (diastole) and away (systole) from the transducer throughout the cardiac cycle (even though there is no murmur) with its onset in early systole, accentuation in late systole and return to baseline only in late diastole. When the SV is placed into the MPA or left PA there is also negative diastolic turbulence, and when the SV is in the DA there is continuous turbulent flow. The flow is at a wide angle in respect to the sample region and may be minimally directional.

The audio signal possesses a classic machinery-like crescendo-decrescendo quality maximal in late systole.

Although not yet proven, in quantitating Qp/Qs for a PDA, pulmonary flow (Qp) may possibly be measured as transmitral flow (PA flow cannot be used as it may lead to underestimation of flow and ratio) or trans Ao flow (in absence of an atrial -ASD- or ventricular septal defect-VSD). Systemic flow, Qs, is measured as systemic venous return and flow across the tricuspid valve or within the RVOT if there is no ASD. Comparing estimated volume flow in the AAo and RVOT or flow across the mitral and tricuspid valves may assess shunt size. In PDA there is reversal of diastolic flow in the DAo below the DA, and in the carotid, cerebral, subcalvian and brachial arteries. With CWD or a velocitometer reversed or decreased flow may be quantitated (R/T ratio). Low velocity continuous flow toward the transducer may occur. In the AAo forward diastolic flow is more pronounced.

In PDA using a 5 MHz transducer and the SV in the AAo, the mean LV output was higher (343 ml/min/kg), and fell rapidly after closure (252 ml/min/kg).

PDA With PH

If the PA pressure is normal there is pandiastolic flow from the DA into the PA. Precordial approach; PWD, CWD and M-mode, from the PDA. A low systolic flow from the Ao to the PA may persist, or a slow velocity flow only in diastole, or a continuous low velocity flow toward the transducer. A reduced, abbreviated diastolic ductal flow with the flow returning to zero before the end of diastole, is a useful indicator of the presence and degree of PH. With Eisenmenger's syndrome and equal Ao and PA pressures, there may be only brief early diastolic flow or even total absence of shunt flow. Tricuspid valve flow velocities are also high, and the PA flow curve less rounded with an early peak and decrease in velocity.

PA pressure may be estimated from a cuff blood pressure, CWD signal and the maximal PA velocity. High velocities may indicate low pressures, and low velocities PH.

Differential Diagnosis

Use two-dimensional echocardiography and PWD. Place SV in bifurcation of the PA and into the DA.

- 1. A PDA can be diagnosed in the presence of other lesions, such as Ao valve lesions and coarctation of Ao (record in the PA as the PDA may not be evident at the DAo).
- A SV placed too close to the PV can produce clicks and artifacts. Aliasing may induce apparent bidirectional flow. From the SSN view and the SV placed in the right PA, normal flow into the LA can be mistaken for PDA flow.
- 3. PR produces a diastolic flow disturbance in the RVOT beneath the PV, of low velocity if the PA pressure is normal. But in the PA, positive usually low flow velocities may be present in diastole too when the PR is significant.
- 4. The combination of a PDA and PR, as in Case 3, has been rarely documented.
- 5. AR, can cause reversed diastolic flow in the DAo and an underestimation of PDA velocity; but there is no systolic flow toward the probe.
- 6. Ao-PA window parasternal short-axis view. Systolic and diastolic flow from the Ao, similar to that of a PDA.
- 7. Coronary artery to PA fistula shows more flow in the mid PA and less at its bifurcation.
- 8. Blalock-Taussig, Waterson surgical shunts. PWD. SSN, high parasternal. May be continuous flow into PA. With SV in PA diastolic anterior and often systolic turbulence; negative systolic and diastolic. SV in right PA- nondirectional spectral broadening in systole and diastole (as in PDA). Direct Doppler detection of flow in a Blalock Taussig shunt may be best- on the right this produced marked continuous turbulence away from the transducer, between the Ao and superior vena cava signals; similar with left to right shunt.

Doppler echocardiography provides high sensitivity, specificity and predictive value in PDA detection in children. Recent studies concluded that combined high resolution, high frequency (7.5, 5 MHz, mechanical scanner) two-dimensional/PWD assessment allows confident detection of both large and small (quantitation) PDAs in preterm infants with lung disease, and provides reliable assessment of ductal size and patency before and after indomethacin therapy in infants.

A PDA in the premature or neonate may produce profound cardiopulmonary deterioration, contribute to respiratory distress and mimic or be associated with pulmonary disease. Ductal shunting may be silent even though large, and clinical findings in PDA may be nondiagnostic.

Acknowledgement

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Case Presentation

Puffer Fish (Tetrodotoxin) Poisoning: Case Report

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Abstract: Tetrodotoxin is an extremely potent neurotoxin found in puffer fishes an several other animals. It acts by selectively blocking the voltage-sensitive sodium channels of excitable membranes of nerve and muscle, causing a rapidly progressive paralysis and death by respiratory failure.

We present a case of puffer fish poisoning in Puerto Rico followed by a review of the literature.

There are about 50 species of puffer fishes, all members of the order Tetraodontiformes. They are variously known as toadfish, blowfish, globefish, swellfish, balloonfish, "fugu" in Japan, "tamborín" and "pez guanábana" in Puerto Rico. These names refer to the ability of the fish to inflate themselves when disturbed to assume a spheroid form almost twice their original size.

These fishes have been known to be very poisonous. The substance responsible for this violent intoxication is known as Tetrodotoxin (TTX), which acts by blocking Na+ ion conductance in excitable membranes.^{1, 2, 3}

Poisoning is caused by ingesting the flesh, viscera or skin of toxic Tetraodontiform fishes. There is a distinct relationship between gonadal activity and toxicity; they are most toxic immediately prior to and during the reproductive season (between May and June).^{2, 4, 5}

We are presenting a case of puffer fish poisoning followed by a review on the subject. It is our interest to alert the medical community of the existence of this species in our waters and the severe, often fatal, intoxication they produce.

Case Report:

A previously healthy 17 year old male caught a puffer fish in the coast of Cataño, Puerto Rico. His mother prepared it and they ate at about 3:30 P.M. Approximately 30 minutes later he complained of numbness and tingling of perioral area and extremities, accompanied by severe dizziness. This was shortly followed by vomiting, diaphoresis, and severe generalized weakness. The

patient was unable to speak although he remained alert. He became agitated and developed severe respiratory distress. On arrival to the Local Health Center he was alert, restless, and with difficulty in swallowing. The patient was treated with Cortisol 100 mg I.M. and referred to the University Hospital (UH). Shortly before arriving to UH he was conscious but showed perioral cyanosis. He arrived to the Emergency Room at 7:45 P.M. in cardiorespiratory arrest. He responed to CPR, was intubated, and a gastric lavage was done. Samples of serum, urine, and gastric lavage were sent for toxicology.

His mother ate a smaller portion of the same fish, developing only perioral numbness.

Vital signs 30 minutes after CPR: heart rate 72/min., blood pressure 90/70 torr, and temperature 35.5°C. He required mechanical ventilation due to absence of spontaneous respirations. There was no response to deep pain, and his pupils were dilated at 8 mm and unreactive to light. Corneal, oculocephalic (doll's eyes), and oculovestibular reflexes were all absent. He was flaccid and areflexic.

The day after admission an electroencephalogram (EEG) showed excessively slow background activity in the theta range. A head computed tomography was normal. When re-evaluated at 6:00 P.M. the patient was still on assited ventilation, but was alert and answered to questions by nodding. He was able to breathe, could open and close his eyes upon request, but there was an external and internal ophthalmoplegia. The corneal reflexes were present but he could not move his extremities and remained areflexic.

At 8:00 A.M. the 2nd. day of admission he could move all his extremities and ocular movements were full. The pupils were isochoric at 4 mm and reactive to light. Deep tendon reflexes were still absent. A spinal tap was normal. Toxicology screening was negative. He was successfully extubated being able to talk. The patient told us he could not remember what had happened after he ate the fish

The 3rd day after admission he was walking about the ward. Neurological examination was completely normal with deep tendon reflexes now +3. An EEG repeated on the 4th day of admission showed no abnormalities. The patient continued asymptomatic except for his aspiration

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pneumonia successfully treated with Amikacin and Mezlocillin. He was discharged after 12 days of hospitalization with no neurologic deficit. A month later the patient continued completely asymptomatic.

Discussion

Epidemiology

The most common cause of TTX intoxication is ingestion of one of the several species of toxic puffers but its occurrence is not limited to them. TTX has been found in certain frogs (gcnus *Atelopus*) from Costa Rica,^{7, 8, 9} in the Pacific goby (*Gobious criniger*),^{7, 8} in the Australian blue-ringed octopus (*Hapalochlaena maculosa*),^{7, 8, 9, 10} and in the Western American newt (genus *Taricha*).^{3, 7, 8, 9, 11, 12}

Poisonous Tetraodontiform fishes are likely to be encountered wherever these fishes occur throughout tropical and semitropical seas. Fishermen in Puerto Rico are familiar with the puffers which they call "tamborín" or "pez guanábana". Due to its repulsive aspect it is not usually eaten. This explains why this intoxication is infrequent here. The authors could find only two reports of fish poisoning from our waters, 13, 14 and neither mentioned Tetrodotoxications. There have been reports of poisoning by puffers in Florida, and toxic puffers have been described in the coastal waters of the United States as far North as New England. The It is interesting that in nearby Haiti, puffer fish is an important ingredient in the formula of the zombi poison.

The geat majority of puffer intoxications occur along the coasts of Asia, especially in Japan. In spite of the toxic nature of the puffers and its recognized ill effects, "fugu", a species of puffer fish, is a delicacy in Japan prepared by licensed puffer cooks.², ⁵, ⁶, ¹⁷⁻²⁰ About 50 cases of poisoning are reported annually in Japan, with a mortality of 61.5%. ², ¹⁷

Toxicology

Organic poisons fall into two broad chemical classes: proteins and nonproteins. TTX is the second most potent nonprotein toxin, the first one being batrachotoxin from a Colombian frog, and ranks fifth in overall potency.¹ The LD₅₀ for mice is 10 ug/kg.^{7, 9, 21} It has been estimated that man is particularly susceptible to TTX poisoning, and an oral dose as low 10 ug/kg may be fatal.²²

Cooking by frying, stewing, baking, boiling, etc., does not inactivate the toxin.² The toxicity of the fish cannot be determined by its appearance or size since even small puffers may contain sufficient poison to be lethal.², ¹⁵ Based on cases of poisoning, the liver, ovaries, and skin, in decreasing order, are considered to be the most toxic parts of the puffer.², ²⁰ The musculature is usually safer to eat, but at times even it may be toxic.¹, ², ⁵, ²⁰

The great majority of cases of Tetradotoxications are accidental poisonings resulting from untrained people, unlicensed cooks, and laymen preparing puffer for their own tables. Unusual cases of homicide by puffer poisoning have been reported.²⁰

TTX's reputation as a highly potent poison is not confined to the scientific literature. lan Fleming had

James Bond paralyzed by TTX in "Dr. No", and in the television series "Columbo" a gourmet chef killed several competitors using an extract from the puffer fish.^{3, 8}

Clinical Manifestations

The onset of symptoms in puffer poisoning vary greatly, depending upon the person and the amount of poison ingested. Symptoms of malaise, dizziness, paresthesias of the lips and tongue, and ataxia most frequently develop within 10 to 45 minutes after ingestion of the fish.1, 4-6, 15, 19, 21 The paresthesias may subsequently involve the fingers and toes, and gradually develop into a severe numbness. Patients have stated that they feel as though their bodies are floating. Sialorrhea, profuse sweating, extreme weakness, precordial pain, hypothermia, hypotension, and a rapid weak pulse usually appear early. Gastrointestinal symptoms such nausea, vomiting, diarrhea, and epigastric pain are sometimes present early, however in some cases they are totally absent. The pupils are constricted during the initial stage and later become dilated. As the clinical picture progresses the eyes become fixed and the pupillary and corneal reflexes are lost.

Shortly after the development of the paresthesias, respiratory distress can become prominent, eventually leading to hypoxia. Petechial hemorrhages, blistering, and subsequent desquamation of the skin have been reported.²

The first areas to become paralyzed are usually the throat and larynx, resulting in aphonia and dysphagia thus presenting as a bulbar paralysis. Later, the muscles of the extremities become paralyzed, and the patient is unable to move. Late in the clinical syndrome an internal and external ophthamoplegia is present. Seizure activity may occur. The victim may become comatose but in most instances remains conscious until shortly before death.², ²¹ Our patient had no memory of the whole incident. This might be due, in part, to transient cerebral anoxia causing a partial retrograde amnesia.

Death results from a progressive paralysis involving the respiratory muscles. If death occurs, it generally takes place within the first 6 to 24 hours. The prognosis is good if the patient survives for 24 hours.², ⁵, ⁶

Fukuda and Tani^{2, 4} staged the syndrome into four phases according to the stages of progression (Table I).

TABLE I

Staging of TTX Poisoning				
Second Degree	: Advanced paresthesia, motor paralysis of extremities, but reflexes still intact.			
Third Degree	: Gross muscular incoordination, aphonia, dysphagia, respiratory distress, precordial pain, cyanosis hypotension, but maintaining consciousness.			
Fourth Degree	: Mental faculties impaired, respiratory paralysis, extreme hypotension, heart continues to beat for a short period.			

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Puffer fish poisoning should not be confused with "ciguatera" poisoning secondary to ciguatoxin, which is endemic in Puerto Rico^{13, 14, 23} (Table II). "Ciguatera" usually produces a much milder disease, although severe intoxications may lead to respiratory failure and death.^{2, 5, 6, 15, 19, 24-27} Two symptoms are probably pathognomonic for "ciguatera". One is a curious sensory misinterpretation in which cold objects feel hot. The other symptom is an itching sensation provoked by alcohol ingestion.²³

tenance of airway and ventilation, (b)maintenance of adequate circulation and renal function, and (c) treatment of cardiac arrhythmia.

Vomiting should be induced if there is no difficulty in swallowing or weakness of the voice. Otherwise, gastric lavage may be carried out after intubation with a cuffed endotracheal tube. Gastric lavage is indicated even if it is more than 3 hours after ingestion, as TTX may delay gastric emptying.^{2, 4, 21}

Any difficulty in dealing with saliva or respiratory

TABLE II

Comparison Between Puffer and Ciguatera Poisoning					
	Puffer Poisoning	Ciguatera Poisoning			
CAUSATIVE FISH	Tetraodontiform fishes (50 species)	More than 400 species of tropical reef fish			
TOXIN	Tetrodotoxin	Ciguatoxin			
SYMPTOMATOLOGY	Rapid onset and extremely violent neurotoxic symptoms: paresthesias, motor paralysis, death by respiratory paralysis. Case fatality rate about 61%.	Onset may be gradual or sudeen. Symptoms mild to severe. Gastrointestinal and neurotoxic, Paresthesias, extreme weakness, joint aches, myalgia and paradoxical sensory disturbance predominate. Case fatality rate about 7%.			

Pharmacology

Action potentials depend on a transient increase in membrane permeability to Na+ ions, allowing an influx of such ions into the cell. TTX prevents the generation of action potentials by selectively blocking the voltage-sensitive sodium channels of the excitable membranes of nerve and muscle.^{1, 2-4, 7-9, 21, 28} This accounts for most if not all the pharmacological actions of TTX and therefore, great part of the symptomatology.¹²

Severe hypotension and respiratory failure are the two major physiological effects of TTX. Hypotension can occur at does as low as 0.5 ug /Kg.⁷ Depression of the vasomotor center,², ⁹, ¹⁷ and/or paralysis of arterial smooth muscle², ³, ⁷, ²⁸ have been implicated as the primary mechanism for hypotension. Large doses of TTX cause failure of myocardial contractility and arrhythmias.², ⁴, ⁹, ²¹

The precise cause of respiratory failure resulting from TTX intoxication remains unresolved. Some investigators have concluded that depression of the central respiratory center is primarily responsible, while others indicate paralysis of the respiratory nerves and muscles as the major contributing factor.^{2, 7, 9, 17, 28}

Due to its selective blocking of Na+ ion conductance TTX has been used extensively in neurophysiology as a research tool.

Treatment

The treatment of puffer poisoning is largely symptomatic since there is no effective antidote for TTX.^{2, 21} Torda et al²¹ proposed a regimen aimed at (a) main-

secretions is an indication for intubation, as is increasing respiratory rate, or progressive elevation of pCO₂. The most effective therapeutic meassure is to provide mechanical ventilation until the toxin is eliminated by natural means.²⁸

Fluid administration should be regulated according to arterial blood pressure, central venous pressure (CVP), and urinary output. Since puffer poisoning result in vasodilation (as well as central cardiac depression in larger doses), the rationale is to infuse plasma expanders until urine output exceeds 40 ml/hr. However, if the CVP rises without restoration of urine output, inotropic agents are indicated.², ⁴, ²¹

The electrocardiogram should be monitored for dysrrhythmias. Atropine is said to be ineffective in preventing TTX- induced bradycardia.²¹ A temporary pacemaker may be necessary when complete atrioventricular dissociation occurs.

Anticholinesterase drugs have been tried with good results by some authors.⁴, ²¹, ²⁹ It is not clear if the observed response from these agents is apparent or real. TTX has no proven effect on the acetylcholine muscle receptors or on actelylcholine release,², ⁴ and other investigators have found cholinesterase inhibitors to be ineffective and even detrimental.², ⁴, ²⁹

Presently the main therapeutic indications are those of supportive and preventive nature; maintaining life support systems until most of the toxin effect has decreased to the point in which the patient can be self supporting.

Resumen: La tetrodotoxina es una neurotoxina extremadamente potente encontrada en los peces tamborín (puffer) y algunos otros animales. Actúa por medio de un bloqueo selectivo de los canales de sodio en las membranas de nervio y músculo, causando un parálisis rápidamente progresiva y muerte por fallo respiratorio.

Presentamos un caso de intoxicación por pez tamborín en Puerto Rico, seguido de una revisión de la literatura.

Acknowledgment

The authors thank Mrs. Concepción S. Fernández for her secretarial assistance.

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50,000 people will be saved from colorectal cancer this year. You can save one.

Save yourself! Colorectal cancer is the second leading cause of cancer deaths after lung cancer. More than 90% of colorectal cancers occur equally in men and women past age 50. Early detection provides the best hope of cure. That's why if you're over 50, you should take this simple, easy slide test of your stool every year. This Stool Blood Test kit is chemically treated to detect hidden blood in the stool and can be done at the time of your periodic health examination so your doctor will know the results.



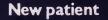
The presence of hidden blood usually indicates some problem in the stomach or bowel, not necessarily cancer. Positive tests must be followed by further testing to find out what the problem is.

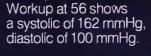
Other tests for colorectal cancer you should talk to your doctor about: digital rectal exam (after age 40); the procto test (after age 50). It is important to report any personal or family history of intestinal polyps or ulcerative colitis, and any change in your bowel habits, which could be a cancer warning signal.

The American Cancer Society wants you to know.



What can you do for hypertensives like Don S?





Dislikes taking medication

Prior to last year, never sick in his life. Hates the thought of yet another medication.

Loves foodBut often eats on

more careful.

the run...vows to be

Coexistent ulcer

Previous physician put him on cimetidine.

Patient description is a hypothetical composite based on clinical experience and evaluation of data.

Rely on one-tablet-a-day dosage and cardioselectivity.*

"Real life" efficacy

Don S represents 899 black patients between 56 and 70 treated effectively in the 28-day TENORMIN evaluation of 39,745 hypertensives of all types. The setting for the evaluation was real life—the daily practices of 9,500 U.S. physicians.¹

Worldwide success

The successful U.S. evaluation came after the efficacy and safety of TENORMIN had already been established worldwide by hundreds of published clinical studies and more than 2 million patient-years of experience.

When the U.S. postmarketing surveillance data were analyzed for variables such as sex, age, race, and weight, a large majority of patients in each group achieved satisfactory blood pressure control, even in Don S's racial and age group.¹

Of all controlled cases, an impressive 95% reported feeling well, an important consideration in hypertension management.²

Compatible with cimetidine and ranitidine

TENORMIN is not metabolized by the liver. Its pharmacokinetics are unaffected when administered concomitantly with cimetidine or ranitidine. This compatibility of TENORMIN with today's widely prescribed $\rm H_2$ receptor antagonists makes it a logical choice for hypertensives like Don S who are under treatment for a coexistent ulcer.

*Cardioselectivity denotes a relative preference for β₁ receptors, located chiefly in cardiac tissue. This preference is not absolute.

A simple regimen for compliance

The simple one-tablet-a-day regimen coupled with a low incidence of side effects⁶ with TENORMIN provided an excellent degree of compliance. Only 15% of the patients in the evaluation reported adverse reactions of any kind, and only 7.5% discontinued therapy.¹



For Don S...and virtually all your hypertensive patients





TENORM (atenolol)

For Don S... and virtually all your hypertensive patients

TENORMIN* (atenolol)

A beta,-selective blocking agent for hypertension

DESCRIPTION: TENORMIN' (atenolol), a synthetic, beta₁-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-12°-hydroxy-3-(1-methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266 ft is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/ml at 37° C and a log partition coefficient (octanol/water) of 0.23 ft is treely soluble in N HCl (300 mg/ml at 25° C) and less soluble in chlorotorm (3 mg/ml at 25° C).

INDICATIONS AND USAGE: TENORMIN (atenolol) is indicated in the management of hyperten-

It may be used alone or concomitantly with other antihypertensive agents, particularly with a

In may be used alone or concomitantly with other antinypertensive agents, particularly with a thiazide-type diuretic.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractifity and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and duretics. TENORMIN should be administered cautiously. Both digitalis and atenoloi slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic. TENORMIN therapy should be withdrawn.

Ischemic Heart Dise asse: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectors and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overflangina pectors, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur. drawal symptoms occur

drawal symptoms occur Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, how-ever, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute the lowest possible dose of TENORMIN should be used, with therapy initiated at 50 mg and a beta;-stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. It treatment is continued, care should be taken when using anesthetic agents which depress the myocardium, such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg., dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg., protound bradycardia, hypotension) may be corrected with atropine (1-2 mg I V).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizaness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg. tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

d be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Impaired renal function (see DOSAGE AND ADMINIST HATION).

Prug Interactions: Catecholamine-depleting drugs (eg. reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked brady-cardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg /kg /day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this tinding. Fertility of male or female rats (evaluated at dose levels as high as 200 mg /kg /day or 100 times the maximum recommended human dose) was unaffected by altenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuo-

lation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atendiol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively)

respectively.

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a doserelated increase in embryo /fetal resorptions in rats at doses equal to or greater than 50 mg/kg or
25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the
maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the
potential risk to the fetus.

Nursing Molbers: It is not established to what event this during excreted in human milk. Since

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (U S studies) or elicited (eg, by checklist—foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo

these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain. The following adverse-reaction data present frequency estimates in terms of percentages: first from the U.S. studies (volunteered side effects) and then from both U.S. and foreign studies (volunteered and elicited side effects):

U.S. STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), tiredness (0.6%-0.5%), tatique (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL diarrhea (2%-0.%), nausea (4%-1%)

RESPIRATORY (See WARNINGS): wheeziness (0%-0.5%), dyspnea (0.6%-1%)

TOTALS U.S. AND FOREIGN STUDIES:

CARDIOVASCULAR bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension

TOTALS U.S. AND FOREIGN STUDIES: CARDIOVASCULAR bradvcardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), light-headedness (3%-0.7%), treaming (3%-1%), tatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%), GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%), RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%), MISCELLANEOUS There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely moni-

be considered if any such reaction is not otherwise explicable. Patients should be closely moni tored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported

POTENTIAL ADVERSE EFFECTS: In addition, a vanety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN (atenolo)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Allergic: Fever, combined with aching and sore throat, laryngospasm and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional liability with slightly clouded sensorium, decreased performance on neuropsychometrics

Gastrointestinal: Mesenteric arterial thrombosis, ischemic collits.

Castroinestinal: Mesenteric anerial informosis, ischemic collis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and loreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the

reaction

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycema. In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodalysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted.

Bradycardia: Atropine or another anticholinergic drug. Heart Block (Second or Third Degree): Isoproferenol or transvenous cardiac pacemaker. Congestive Heart Failure: Conventional therapy. Hypotension (Depending on Associated Factors): Epinephrine rather than isoproferenol or norepinephrine may be useful in addition to altropine and digitalis.

Bronchospasm: Amnophylline; isoproferenol, or altropine.

Hypoglycemia: Intravenous glucose.

Bronchospasm: Arminophylline, isoproterenol, or atropine. Hypoglycemia: Intravenous glucose DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diurent therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit. TENORMIN may be used alone or concomitantly with other antihypertensive agents including this artise, but daily and alpha-methyldona.

thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance talls below 35 ml/rmin 1.73 m² (normal range is 100-150 ml/rmin/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment.

Creatinine Clearance (ml min. 1.73 m²)	Atenolol Elimination Halt-life (hrs)	Maximum Dosage	
15-35	16-27	50 mg daily	
<15	>27	50 mg every other day	

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur. HOW SUPPLIED: Tablets of 50 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 105 embossed on the other side are supplied in monthly calendar packages of 28 tablets, bottles of 100 tablets, and unit-dose packages of 100 tablets. Tablets of 100 mg TENORMIN (atenolol) round, flat, uncoated, white tablets with Stuart embossed on one side and NDC No. 101 embossed on the other side are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets. Protect from heat, light, and moisture. Store unit-dose and calendar packages at controlled room temperature.

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Medicolegal Decisions



MOTHER SUES PHYSICIAN FOR REVEALING HER IDENTITY TO ADOPTEE

A mother had a cause of action for breach of confidential relationship against a physician who revealed her identity to the daughter she had given up for adoption, the Oregon Supreme Court ruled.

The 21-year-old daughter sought out the physician when she wanted to establish contact with her biological mother. The physician gave the daughter a letter stating that it was important for her to find her biological mother because he remembered giving her diethylstilbestrol (DES). This statement was untrue and was made only to help the daughter breach the confidentiality of the records of her birth and adoption. Hospital personnel, relying on the letter, permitted the daughter to make copies of her mother's medical records, which enabled her to locate her mother.

The mother brought an action against the estate of the physician, who had died. The trial court entered judgment for the estate. An appellate court reversed on counts of breach of aconfidential relationship and invasion of privacy.

On review, the Oregon Supreme Court said that if the mother had a claim, it arose from a breach of a professional duty to keep her secret rather than from a violation of her privacy. The court said that the claim was not that the physician had pried into a confidence but that he had failed to keep one.

The court pointed out that in a number of decisions it had been held that unauthorized and unprivileged disclosure of confidential information obtained in a confidential relationship could give rise to damages. The court agreed with the appellate court that the mother could proceed under her claim of breach of confidentiality in a confidential relationship. The court reversed the appellate court's decision with respect to the claim of invasion of privacy and affirmed as to the claim of breach of confidence and sent the case back for further proceedings.—Humphers v. First Interstate Bank of Oregon, 696 P.2d 537 (Ore.Sup.Ct., March 6, 1985)

\$137,000 VERDICT AGAINST SURGEON REVERSED BY COURT

A verdict of \$137,000 against a surgeon should be reversed, an Ohio appellate court ruled.

A patient elected to have plastic surgery on her right hand to improve movement in her middle finger. Her finger had been badly scarred in a fire when she was three months old, but she was still able to perform many functions with it. Her ring finger was also deformed but it did not hinder movement of the middle finger. The surgeon told her that a skin graft would be necessary and that he would extract the needed skin from her buttocks. He also told her that there may be circulation problems in the middle finger. She signed a consent form to the procedure.

The day after the operation, she was in great pain and asked the surgeon what was causing it. He informed her that he had removed the right ring finger because it was in the way and to obtain the skin necessary for the graft. The patient testified that she became hysterical over this information and was sedated. She said that her middle finger was less flexible after the operation and that she had no feeling in it. She claimed that she had never been told that her ring finger would be amputated or that there was a chance her middle finger would actually be less mobile. The surgeon testified that he told the patient that he would remove the ring finger and that complications could result in the loss of the middle finger.

In a suit against the surgeon for negligence and battery, a jury returned the verdict of \$137,000 in favor of the patient, and the surgeon appealed.

Reversing the decision, the appellate court said that the trial court erred in instructing the jury. The physician requested that the court ask the jury to specifically answer questions whether the patient had been advised that her right ring finger was going to be removed and whether she had been advised of all material risks attendant to surgery.

Although the patient did not call any expert witnesses of her own, she established her claim through cross-examination of the surgeon, the court said. The case was remanded for further proceedings.—Ware v. Richey, 469 N.E.2d 899(Ohio Ct. of App., Dec. 27, 1983)

SURGEON NEGLIGENT IN TREATING EYE PROBLEM

A minor patient was not entitled to an increase in the \$23,000 in damages she was awarded for negligence by a surgeon in treating her congenital eye deficiency, the Utah Supreme Court ruled.

When the patient was six months old, she was discovered to have been born with congenital esotropia. That condition affected both eyes and was followed by amblyopia. The surgeon treated the youngster periodically and performed two operations on her. A second physician discovered that a lateral rectus muscle had apparently been cut in one of the earlier surgeries. The eyes were ultimately corrected so that she would have 75 per cent normal rotation use of the affected eye.

The jury was instructed that the surgeon had conceded liability, and it awarded the patient \$23,000.

On appeal, the patient argued that the award was inadequate. The Supreme Court said that the judgment should be affirmed. The court noted that an outpatient routine could treat the problem easily with a high expectation of success. The court denied the patient's request to increase the amount of the damage award.

—Meyer v. Bartholomew, 690 P.2d 558(Utah Sup.Ct., Oct. 1, 1984)

NEW TRIAL FOR SUIT FOR UNNEEDED HYSTERECTOMY

A patient was entitled to a new trial of her claim against a physician on the theory that the physician failed to disclose that hormonal therapy was an alternate treatment to a hysterectomy, the Oklahoma Supreme Court ruled.

During the hysterectomy, the patient's bladder was inadvertently cut or punctured. The bladder injury was properly repaired. The patient filed suit against her physician on grounds that the physician was negligent in injuring her bladder and that the hysterectomy was unnecessary. A trial court entered judgment in favor of the physician, and the patient appealed.

On appeal, the Oklahoma Supreme Court said that the patient failed to establish a case of negligence by the physician. The patient presented no expert testimony to the effect that the physician failed to meet the applicable standard of medical care. The patient argued that the physician's postoperative notes, which stated that there had been an "inadvertent entry of bladder," was sufficient to an admission of negligence. The Supreme Court said that was not an admission that the care was substandard, and the patient's negligence claim should fail for lack of expert testimony.

The court upheld the patient's claim that she could recover under a theory of lack of informed consent. The patient claimed that the physician did not inform her that

hormonal therapy was an alternative to the hysterectomy. The patient testified uncquivocably that had she been told of the alternative of hormonal therapy she would not have consented to surgery. The court said that the trial court erred in directing judgment in favor of the physician.

The court remanded the case for a new trial on the theory of informed consent.—Smith v. Karen S. Reisig, M.D., Inc., 686 P.2d 285 (Okla.Sup.Ct., July 24, 1984; as corrected, Aug. 2 and Aug. 13, 1984)

NEW TRIAL FOR SUIT FOR NEGLIGENT HYSTERECTOMY

A patient was entitled to a new trial of a claim of negligence during a hysterectomy, the highest court of Massachusetts ruled.

The patient's ureter was injured during the course of a hysterectomy, causing pain to the patient and requiring corrective surgery. During the trial of her malpractice claim against the operating physician, she presented expert testimony that a suturing procedure used by the physician attempting to control bleeding on the left side of her uterus did not conform to good surgical practice and caused the damage to the ureter. The physician's medical expert gave his opinion that the physician's operative procedure complied with the accepted standards of care at the time of the surgery. A jury returned a verdict in favor of the physician. An appellate court affirmed.

Reversing the decision, the high court said that the trial court erred in its instructions to the jury. During its instructions, the court had instructed the jury that expert testimony was necessary to establish the physician's negligence. During the course of the trial conflicting evidence was admitted concerning an admission allegedly made by the physician. According to the patient and her husband, after the operation he told them that he had made a mistake during the hysterectomy and severed her ureter. The court did not instruct the jury that the alleged admission, if the jury believed that it was made, was sufficient by itself to support a verdict in favor of the patient.

Failing to give the jury that instruction placed undue emphasis on the expert testimony and may have left the jury with the erroneous impression that they needed the expert testimony in addition to the admission by the physician in order to find him liable, the court said. The case was remanded for a new trial.—Collins v. Baron, 467 N.E.2d 171 (Mass.Sup.Jud.Ct., July 30, 1984)



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ACTIVOS

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AFILIADOS

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Sanz, Carmen Zoraida, MD - Escuela de Medicina Cayey, 1982, Psiquiatría.

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Abstracts	
AMERICAN COLLEGE OF PHYSICIANS PUERTO RICO REGIONAL MEETING	
OCTOBER 1985	

PARTIALLY TREATED MENINGITIS IN ADULTS: A PROSPECTIVE STUDY OF 102 PATIENTS. Carlos H. Ramfrez-Ronda, M.D., F.A.C.P. and Hector F. Gorbea, M. D., Member, University of Puerto Rico School of Medicine and VA Medical Center, San Juan, Puerto Rico.

Patients (PTS) that present to the hospital with meningeal signs after receiving antibiotics (AB) prior to the initial evaluation represent a challenge in management. The present study was designed to evaluate in a prospective manner if the management criteria derived from a retrospective study of PTS with partially treated meningitis (PTM) are useful. PTS with meningitis (M) and history of receiving AB for >48 hrs were managed as bacterial (BAC). Those with A8 treatment for < 48 hrs and not alert were treated as BAC; the alert PT was observed, and if at any time the CSF findings showed a sugar ratio of ≤40%, protein ≥150mg% or WBC count ≥1200 cells/mm on initial or repeat LP, they were managed as BAC, the rest were observed and sent home. 102 PTS with PTM were followed prospectively. There were 55 males, mean age of 41 yrs, and 47 females, mean age of 43 yrs. 14/104 PTS received A8 therapy for ≤ 48 hrs prior to initial LP. All 14 were not alert and were treated with AB; 13/14 were cured and 1 died of epidural abscess. 8B/102 received AB for <48 hrs prior to initial LP. 20/8B were not alert; all 20 were treated with AB, 5 died of pneumococcal meningitis (PM). 68/88 PTS were alert. Six of the 68 had initial LP with BAC criteria, all 6 were treated, 1 died of PM. Of the remaining 62, 2 had cryptococcal M and were treated accordingly, 1 died. The remaining 60 PTS were observed and all had an LP repeated in 6-18 hrs. Three had a second LP with changes repeated in 6-18 hrs. Three had a second LP with changes toward BAC criteria. 57/60 who were observed had a repeat LP revealing no BAC criteria; these PTS were observed without AB therapy, all survived. Length of hospitalization for observed PTS was from 4-6 days while for treated PTS was 14-21 days. Adult PTS with PTM who receive AB for 4B hrs before initial LP, who are alert, and CSF findings lack the criteria for BAC M may be observed and LP repeated in 6-12 hrs. If the repeat LP do not show changes toward 8AC M, the PTS may be observed closely without A8 therapy. This results in considerable cost savings and the PTS are not exposed to the risk of AB side effects.

ENDOSCOPIC VARICEAL SCLEROSIS:SAN JUAN CITY HOSPITAL EXPERIENCE Martin Ortiz M.D. (Associate), Edwin Melendez M.D., Rodolfo Rodriguez M.D., Esther A. Torres MD (Member)San Juan City Hospital, San Juan, PR.

Nineteen patients with variceal hemorrhage, Child's class A(4),B(9),C(6) were treated with endoscopic variceal sclerosis(EVS), and followed for up to one year Eight sclerotherapy sessions were done in 5 patients during active bleeding with complete control of bleeding in all.

Nineteen patients underwent elective EVS in 57 sessions. Ten patients rebled(52.6%). Rebleeding in the same hospitalization before EVS was 31.5% and 10.5% after EVS. Rebleeding according to Child's classification was: A-25%, B-33%, C-100%. Complications of EVS were chest pain(42.1%), fever(15.8%), esophageal ulcers (31.6%), dysphagia(5.3%), abnormal Chest XRay(10.5%) and bacteremia (5.5%). Overall mortality during follow upperiod was 31.5%, none felt to be related to EVS. Causes of death were UGI bleeding and hepatic coma. All deaths were on Child's C patients. Overall survival was 68.5%.

EVS is effective in the control of variceal hemorrhage in active bleeding and prevention of rebleeding, with few complications and adequate survival. Major morbidity and mortality ocurred only in Child's C patients.

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ACQUIRED FACTOR VIII DEFICIENCY IN ESSENTIAL THROM-BOCYTHEMIA. Daled Bahri, MD (Associate), Aida Fernández, MT, Marly Mignucci, MT, Sherley McCurdy, MT, Francisco Muñiz, MD, And Francisco Robert, MD (Member), Veterans Medical Center, San Juan, Puerto Rico.

Coagulation factor deficiencies have been described in chronic myeloproliferative disorders (CMD). We recently identified a patient with essential thrombocythemia (ET) and factor VIII deficiency. Evaluation of possible causes of factor VIII deficiency was performed in this patient, and results were compared with coagulation profiles done in patients with CMD, reactive thrombocytosis (RT) and normal subjects. Factor VIII kinetic studies were performed in this patient using intravenous infusion of 1-deamino-8-darginine vasopressine. Low values of factor VIII coagulant activity were found when this patient was in relapse, and normal levels were detected during remission. Kinetic studies suggested an increase clearance of factor VIII coagulant activity during relapse. Coagulation profiles in patients with CMD and RT revealed the following: (1) patients with CMD had lower levels of Factor V (p<0.05), as compared with patients with RT and normal subjects, and (2) patients with RT did not have any coagulation factor deficiencies. This study has shown that factor VIII deficiency in our patient with ET has an acquired deficiency. The response to cytoreduction and the factor VIII kinetic data suggest that this deficiency appears to be associated with a large myeloid-megakaryocytic cell mass characteristic of this disorder. Increased number of normal intravascular platelets per se is not associated with significant adsorption of clotting factors.

EFFICACY OF ORAL VS. INTRAMUSCULAR STEROID IN THE TREATMENT OF ACUTE ASTHMA. Ivelisse Ramirez, MD (Associate), Awilda Maldonado, MD (Associate), Noel Totti, MD. Veterans Administration Hospital, San Juan, Puerto Rico.

Steroids are effective in the treatment and prevention of acute bronchial asthma attacks. However the efficacy of a single dose of an intramuscular long acting steroid in the prevention of recurrent bronchial attacks has not been studied. In this study the efficacy of intramuscular triamcinolone is tested against a short course of oral prednisone in a double blind randomized fashion. Ten patients entered the study. Respiratory function was evaluated prior to institution of standard therapy for bronchial asthma. At the time of discharge five patients received triamcinolone and five patients received prednisone. Respiratory function upon discharge from emergency room was not significantly different among the patients. At reevaluation 14 days later patients on prednisone remained more symptomatic and required further emergency care than patients on triamcinolone (p<.05). The triamcinolone group had 76% of their predicted FEV 1 as compared to 45% in the prednisone group (p<.05). Age, total eosinophil count and immunoglobulin E levels were not significantly different among the groups. It is concluded that a single dose of intramuscular steroid is more effective than a tappering course of oral steroids in the prevention of recurrent asthma attacks.

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CLINICAL AND SEROLOGIC PROFILE OF SERONEGATIVE SPONDYLOARTHRITIS IN PUERTO RICO. Ramón Arroyo, MD, Edna Nettleship MT, Edwin Mejías, MD. Veterans Administration Hospital and University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

The seronegative spondyloarthritis comprise a group of disorders including Ankylosing Spondylitis (AS), Reiter s syndrome (RS) and Psoriatic Arthritis (PsA), characterized by its association with the histocompatibility antigen (HLA)-B-27. We have performed a retrospective study in 73 patients followed by us to determine: (1) Clinical characteristics of AS and related disorders in Puerto Rico (PR) (2) If our population follows the previously described HLA-B-27 association or (3) If in view of our heterogeneous ethnic background another marker is present. Our results show that: (1) No differences in clinical picture and radiologic findings when compared to other ethnic groups (2) HLA-B-27 was found in 67% of HS and 43% of AS in contrast to 95% and 60-80% in white Americans respectively. (3) There were no differences in HLA-B-27 for PsA. (4) HLA-A2 was present in 63% of patients with Rs. From our studies we conclude that: (1) HLA-B-27 is not as a good marker for our patients with AS&RS as it is in American whites (2) The HLA data in our group with AS&RS is very similar to that of American blacks (3) In PsA, HLA-B-27 was similar to other groups (4) The higher frequency of HLA-A2 in RS may be associated with the ocular involvement of anterior uveitis seen in this disease and its relation to this antigen and not necessarily a marker for RS.

MECHANISMS OF RESISTANCE AMONG AMIKACIN-RESISTANT STRAINS RECOVERED IN AN INSTITUTION OVER A 3-YEAR PERIOD OF AMIKACIN USE AS A FIRST LINE AMINOGLYCOSIDE. Sonia Saavedra, M.O., Member, Carlos H. Ramfrez-Ronda, M.O., F.A.C.P., Doris Vera, M.T., Rosa Fernández, Lillian Cardona, and Miguel Villar. University of Puerto Rico School of Medicine and VA Medical Center, San Juan, Puerto Rico.

Amikacın was instituted as the first line aminoglycoside at the San Juan VA Medical Center in January 1982. next 3-year amikacin-usage period (1982-1984), a total of 84 out of 3617 gram-negative isolates was found to be resistant to amikacin by both disk and microdilution methods, for an overall resistance of 2.3% during this period. The mechanisms of resistance have been studied in 22 strains; 18 Pseudomonas aeruginosa, one Serratia marcescens, one E. coli, and two Klebsiella pneumoniae strains. Among the 18 Pseudomonas aeruginosa strains resistant to amikacin, 7 were found to be by changes in permeability; the mechanism resistance in the remaining 11 strains was enzyme production. Six strains were found to produce only aminoglycoside acetyltranferase 6'I (AAC 6'I); two strains were found to produce aminoglycoside phosphotranferase 3' II (APH 3' II); two strains were found to produce two different enzymes, AAC 6'I and APH 3'II, and one strain was found to produce three different enzymes, AAC 6'I, APH 3'II and aminoglycoside nucleotidyltransferase 2" + (ANI 2" +). The Serratia pneumoniae strains were found to produce three different enzymes, AAC 6'I, APH 3'II and aminoglycoside phosphotransferase 3'I (APH 3'I). The strain of F colistudied was resistant by marcescens studied was found to produce an aminoglycoside studied was resistant by permeability changes. Among the Pseudomonas aeruginosa strains studied, when analyzed by year the mechanism of resistance by enzyme production AAC 6'I has been steadily increasing and in 1984, amıkacın-resistant <u>Pseudomonas</u> <u>aeruginosa</u> strains studied were enzymes producers. In a hospital where amikacin has been used as the first line aminoglycoside for over 3 years, the overall amikacin resistance has not changed; there is a tendency of individual year increase in resistance. The mechanisms of individual year increase in resistance. resistance of the amikacin-resistant strains were mediated by enzymes in 64%, and 50% of the studied strains were producers of AAC 6'I.

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INCIDENCE OF COLLAGEN DISEASE IN PATIENTS WITH CHRONIC URTICARIA. José N. Moreno, M.D., ACP Member, Bayamón, Puerto Rico.

Chronic urticaria is one of the most challenging problems for the clinician. It has been stated that after extensive evaluation, the etiology is idiopathic in up to 80% of the cases studied. The following data represents the experience of the author in private practice.

Of 249 patients that were evaluated for chronic urticaria, twenty seven presented with positive ANA (10.8%). Their titers went from 1:20 up to 1:1270. The pattern was homogeneous in 13/27; speckled in 10/27, homogeneous and speckled in 2/27 and nucleolar in 2/27.

Two of the 27 patients with positive ANA developed SLE and six of the 27 have undifferentiated collagen disease; one has mixed collagen disease. Both the patients with undifferentiated collagen disease as well as the one with mixed collagen disease have done well on antihistamines.

Twelve out of the 27 patients with positive ANA (44% have normal complement levels. Eight of the twelve patients mentioned previously have evidence of dermographism by skin test with positive history of pressure urticaria. Fifty eight percent of them have responded well to antihistamines.

The patients' symptoms, laboratory work-up and res-

The patients' symptoms, laboratory work-up and response to treatment will be presented in tables.

GUILLAN BARRE SYNDROME: INCIDENCE, MAJOR COMPLICATIONS AND OUTCOME AT SAN JUAN VETERANS ADMINISTRATION HOSPITAL. Rafael Meléndez, MD, Valerie Wojna, MD, Veterans Administration Hospital, San Juan, PR.

From January 1975 to December 1984 25 patients were admitted to the PR VAH with a clinical picture of GBS, only 15 patients had a final diagnosis of GBS. Two of these patients had recurrence within the same time of the study, and one patient had ${\boldsymbol a}$ Chronic Relapsing Type. The incidence of GBS was highest in the 30-to 50- year old age group at VAH being a younger group when compared with other epidemiologic studies done at US. The frequencies of antecedent respiratory (41%) and gastrointestinal (6%) illness exceeded frequencies of such illness in the US population. Cranial nerve involvement was seen in 8 patients, were VII and XII were more affected. The most common complications found were autonomic Dysfunction, Pneumonic Process (both with 29%) and Respiratory Failure (24%). Complete recovery was seen in 64%, incomplete recovery in 30% and one patient died. Most treatment was supportive but 4 patients received steroids, no significant difference was found when compared to outcome except for a marked improvement in the chronic relapsing type after steroid therapy.

CANOIDA TROPICALIS IN ACUTELY ILL PATIENTS. Julie R. Rodríquez, M.D., Member, Héctor F. Gorbea, M.D., Member, María Medina, M.S., and Carlos H. Ramfrez-Ronda, M. D. F.A.C.P. University of Puerto Rico School of Medicine and VA Medical Center, San Juan, P. R.

During a 36-month period, 32D Candida spp. were recovered from patients (PTS) at the San Juan VA Center. Of these, 31.8% were Candida tropicalis (CT). The isolation of this organism has increased through the years, 15.5% of all Candida spp. in 1982, 33% in 1983 and 42.5% in 1984. The clinical implications of these findings were not known, so we studied these PTS for the years 1982 and 1983 (24-month period). Forty-five records of PTS with positive cultures for CT were evaluated, Forty-four PTS were male and 1 was a female. The mean age of these PTS was 68 years (range:35-96 years). Ouring 1982, 10/11 PTS were evaluated; of these, 8 PTS had cardiovascular disease, 3 had Diabetes mellitus, 2 had a cerebrovascular accident and none had a solid or hematogenous malignancy. In 1983, of the 35 PTS with CT evaluated, 11 PTS had a recognized malignancy, 7 had Diabetes mellitus and 2 had a cardiovascular disease. All PTS except 7 received broad spectrum IV antibiotics prior to positive cultures for CT. The underlying infections for which parenteral antimicrobial therapy were given included pneumonia (64%), UTI (27%), endocarditis (8.6%), soft tissue or bone infection (5.6%), and neck abscess (2.8%). Other risk factors were IV lines in 84%, foley catheters 20%, parenteral hyperalimentation 11%, and steroid therapy 9%. CT was recovered from urine in 29 PTS, from sputum in 14, from soft tissue in 2, and 1 each from lung tissue, pleural fluid and chest wound, and from blood. Only 4 PTS received therapy with amphotericin 8, (2 IV therapy and 2 urinary irrigations). Mortality of PTS from which CT was recovered was 64% (90% in 1982 and 55% in 1983). In none of the cases was this potential pathogen recognized as the cause of the demise. CT in the cases reported here was not considered a major pathogen; this may need reevaluation since it is recovered from PTS with underlying illnesses and associated in these PTS with high mortality. The recovery of CT from a seriously-ill hospitalized PT needs reevaluation and may indicate a neg

CRYPTOSPORIDIUM: CELLULAR LOCALIZATION AND STRUCTURAL ANALYSIS OF ABSORPTIVE CELL-PARASITE MEMBRANE-MEMBRANE INTERACTIONS. Manual A. Marcial, M.D. and J.L. Madara M.D. Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston. Intestinal infestation by cryptosporidia has recently been associated with diarrhea in humans. However, the anatomy of the interaction between the parasite and absorptive cells is imprecisely defined. In ilea of spontaneously infected guinea pigs, we defined the cellular localization of the parasite and examined the interface between the parasite and absorptive cell microvillus membranes using high resolution thin section and freeze fracture techniques. We utilized the distinctive life cycle stages of the parasite to delineate the sequence of structural alterations which follow Cryptosporidium-absorptive cell association. Cryptosporidium displays one outer and two inner plasma membranes and initially appear to associate with microvillus tips. Subsequent flattening of the microvilli produces redundant folds of microvillus membranes which envelop the parasite and later fuse at a site over it. This results in the intracellular localization of the parasite within a sphere of internalized micrivilli membranes which separates the organisms from the host cytoplasm. Other changes occur with further maturation of the Cryptosporidium. The observations to be presented allow the following conclusions: 1) that the parasite is intracellular; 2) that it initially penetrates absorptive cells and that the parasite is surrounded by microvilli membranes; 3) that subsequent fusion between microvilli membranes and outer membranes isolate the site at which Cryptosporidium "feeding organelle" develops and associates with host cytoplasm, and 4) that it may be transported across the intestinal epithelium by M cells and subsequently phagocytosed and processed by macrophages.

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ATYPICAL PRESENTATION OF BURKITT'S LYMPHOMA ASSOCIATED WITH ANTIBODY AGAINST THE HUMAN T-CELL LEUKEMIA LYMPHOMA VIRUS (HTLVIII) Gladys I. Rodriguez, MD, Francisco Robert, MD, (Member) Luis Báez, MD and Francisco J. Muñiz, MD, Veterans Administration Hospital, San Juan, Puerto Rico.

High grade Non Hodgkin's Lymphomas have been increasingly associated with the acquired immunodeficiency syndrome (AIDS). Burkitt's Lymphoma is among these agressive lymphoproliferative disorders. We have recently studied two such patients with an atypical clinical presentation.

One patient is a 56 year old male with a history of drug abuse for 30 years, who presented with a rapidly growing right thigh mass. A muscle biopsy revealed an undifferentiated Burkitt's Lymphoma, which was also found in a bone marrow biopsy.

Another patient is a 38 year old bachelor presenting with peripheral neuropathy and ophtal-moplegia. Bone marrow and lymph node biopsies where characteristic of Burkitt's Lymphoma. Spinal fluid and peripheral blood examination revealed Burkitt's cells.

HTLV III antibody Elisa test was positive in both patients. They were treated with agressive combination chemotherapy which included the central nervous system. Our first patient had a partial response. The second patient responded transiently with a rapid relapse. These cases underline the need to evaluated all lymphomas with atypical manifestations for incidence of exposure to HTLV III and clinical features of AIDS.

CORRELATION OF SEROLOGICAL AND COPROLOGICAL PARAMETERS IN 17 PATIENTS WITH CHRONIC SCHISTOSOMA MANSONI (SM) INFECTION. Hector F. Gorbea, M.O., Member, George V. Hillyer, Ph. D., Julie R. Rodríquez, M.D., Member, Guillermo Vázquez, M.D., and Carlos H. Guillermo Vázquez, M.D., and Carlos H. Gramfrez-Ronda, M.D., F.A.C.P. UPR School of Medicine and VA Medical Center, San Juan, Puerto Rico.

An ongoing longitudinal, non-randomized, open study was designed to evaluate the coprological and serological parameters in 17 adult patients (PTS) with chronic SM infection before and after treatment with praziquantel (PZQ). Eight female and 9 male PTS with a mean age of 32 years and positive stool examination for SM were enrolled in this study. Quantitative stools for 0 and P (Ritchie's method), Circumoval Precipitin Test (COP) and COP antigen (Ag) by ELISA were performed in all PIS. All PIS were treated with PZQ at a dose of 15 mg/kg total body weight orally T.I.D. for a single day. The PTS orally I.I.D. for a single day. orally 1.1.0. for a single co, are reevaluated at 2 wks and at 1, 3, 6, are reevaluated at 2 wks and at 1, 8, 6, 12 and 18 months post-treatment. show a mean pretreatment egg count of ova/g of stools and all PTS demonstrated a positive COP. By 2 wks post-therapy, a 100% coprological cure was documented which has persisted during follow-up. The COP, however, has remained positive in 9 out of 13 PTS at 12 months post therapy. COP Ag by ELISA remained positive in 15 out of 15 PTS at 6 months post therapy. Preliminary results reveal a lack of serological agreement be tween coprological parameters in these PTS with chronic SM infection treated with PZQ.

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COMPARATIVE IN VITRO ACTIVITY OF BMY 28142 (BMY), HR-810 (HR), RO-17230 (RO), AZTREONAM (AZT), CEFOTAXIME (CFT), IMI-PENEM (IMP) AND TICARCILLIN-CLAVULANIC ACID (TC-CL), AGAINST AMIKACIN-RESISTANT (AKR) AND AMIKACIN-SUSCEPTIBLE (AKS) BACTEREMIC STRAINS OF PSEUDOMONAS AERUGINOSA. Carlos Rivers-Vázquez, M.D., Minerva Nevárez, M.T., and Carlos H. Ramírez-Ronda, M.D., F.A.C.P. University of Puerto Rico School of Medicine and VA Medical Center, San Juan, Puerto Rico.

The in vitro activity of BMY, HR, RO, AZT, CFT and IMP against $\overline{25}$ each bacteremic clinical isolates of AKR (MIC ≥ 32 $\mu g/ml)$ and AKS (MIC ≤ 16 $\mu g/ml)$ Paeudomonas aeruqinosa was studied and compared. The MIC was determined using the MIC 2000 System with an inoculum of 10 to 5×10^5 CFU/ml. All media was adjusted for calcium and magnesium. All susceptibilities were determined simultaneously and in duplicate, using standard powders diluted as per manufacturers instructions. All AKR strains were resistant to gentamicin, tobramycin and netilmicin. The MIC $_{50}$ and MIC $_{90}$ were as follows:

Antibiotic	MIC _{SO} ug/ml		МІС ₉₀ µg/ml	
	AKR	AKS	AKR	AKS
BMY	16	2	32	2
HR	16	4	32	4
RO	16	2	16	2
AZT	32	4	64	4
CFT	128	16	>128	32
IMP	2	1	4	2
TC+CL	128	16	128	32

TC+CL 128 16 128 32 The activity of BMY, HR, RO and AZT against AKS strains was comparable with MIC $_{\rm SO}$ $\stackrel{<}{\sim}$ 4 $\mu g/ml$, the activity of TC+CL was similar to that of CTI. IMP was the most active agent. For AKR strains the most active agent was RO followed by BMY and HR (MIC $_{\rm SO}$ 32 $\mu g/ml$); the activity of CTI and TC+CL was negligible against these strains. The new betslactamic agents offer possible alternatives for the transment of infections caused by AKR strains if proven effective in clinical studies.

POST-SURGICAL HYPOPARATHYRODISM (PSHP): UNIVERSITY HOSPITAL EXPERIENCE. V. Rabell, M. D.(Member), F. Aguiló Jr., FACP, M. Vázquez, H.T., & Supporting Staff, Endocrine Div., Surgery & Pathology Depts., University of P. Rico School of Medicine, S. Juan, P.R.

PSHP, resulting from damage to the parathyroid glands during thyroid or parsthyroid surgery, was identified in 22 patients during the period 1967-1984 in 277 operatione, a 7.9% incidence. A higher proportion of thyroid cancer patients (12%) had PSHP, in relation to 8% for thyrotoxicosis and 5% for hyperparathyroidism. In 58 additional operations for nodular goiters during 1980-84, there was only one instance of PSHP (1.7%).

Transient hypocalcemia (THCa) occurred twice ae frequently among thyrotoxic patients (4/23 = 17%) than among those operated for nodular goiters (5/60, 8%), presumably due (at lesst partly), to the presence of thyrotoxic oeteodystrophy.

The most common symptoms and signs of PSHP or THCa, in decreasing order were: provoked Chvostek sign (61%); spontaneous or induced Trousseau (50%); perioral numbness (44%) and tingling sensation of hands (39%). Onset of documented hypocalcemia among cases of THCa was econer (within 24hrs) than among PSHP (within 48hrs post-op.). The mean nadir serum calcium found among the thyrotoxic group was 5.2 mgs/dL.

Definitive treatment with vitamin D was instituted for PSMP after a mean observation period of 2.75 months (range: 8 days to 11 months), usually requiring from 50,000 to 150,000 units/day. Due both to the variability of dosage requirements and to the unexpected cases of vitamin D intoxication, these patiente must be monitored at fairly frequent intervals for life.

Our institutional incidence of PSHP is within that reported in the literature, which has varied from 0.5% (friesen) up to about 20% (Robins, Gordan). Only once, in 1977, was there an excessive number of PSHP, probably due to a change in surgical policy of the intervening surgical team in treating thyrotoxicosis. This emphaeizes the need for well-defined, fairly uniform institututional criteria in management of neck surgery where risk of PSHP exists. This hae decreased the number of PSHP during the past 4 years.

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Fine Needle Thyroid Aspiretion: Our Preliminary Studies at UOH. O.DIAZ* F.AGUILO, R.ROORIGUEZ, G.VILLAMARZO, W.ROORIGUEZ, F.SILVA, E.VAZQUEZ-Q., M.ALLENDE, V.RABELL & F.BACO. Endocrine Oiv., Cytopathol., Sonography, Nuclear Med. & Surg. Opts. UPR

Eighty (80) patients with thyroid nodules with (\bar{c}) or without (\bar{s}) goiter were submitted to 88 FNTA biopsies. Most [74, 92.5%] were female & mean age 43 (range 17-74 yrs) and ave. duration of a node = 15 months. Cytological diagnoses (0x) on a surgerized S group of 34 (42.5% of total) were: cancer (4), benign (14), "suspicious" (11) and inadequate or non-0x (5). Three of 4 CA's were confirmed at operation, there was one false positive, I false negative and I occult CA. Two of the 6 CA patients were or had been thyrotoxic; 24/34 c "neg." cytologies were true negatives. Among 5 non-0x, 4 were benign and I had occult CA. The non-surgerized (NS) group of 46, as compared with the S group showed a tendency to be older (46 vs. 38 yrs), having goiter (48% vs 38%) shorter duration of node (12.5 vs 18 mo.) & higher positivity for antimicrosomal antioodies (26% vs 13%). Both groups were similar as to prevalence of a cold nodule on radioisotopic scan (S, 87%, NS, 81%), solid mass by sonography (S, 56%, NS, 49%) or previous neck irradiation (0, 2%). No morbidi ty was encountered and patient's acceptance was excellent. Along the study, we have gained considerably in skill and confidence. More operations will be needed in order to assess sensitivity/specifity by ou group, especially on single cold nodules.

MORTALITY FROM DIABETES IN PUERTO RICO AND FROM DIABETIC COMA AT THE UNIVERSITY HOSPITAL: SOME PUZZLING FINDINGS. F. Aguiló Jr. FACP, M. Allende (Member), & Supporting Staff Endocrine Division, UPR School of Medicine

Ourlng 1950 through 1970, mortality due to Diabetes mellitue (OM) in PR climbed eteadily, in a mannar similar to the non-white USA population, reaching 26.4 per 100,000 population. It then decreased to a nadir of 16.6 in 1977, when again it rouse eteadily to an all-time high of 31 per 10⁵ in 1983. (In the meanwhile, USA mortality continued ite downward pace from 15.3 to 11 x 100,000). In order to investigate the possible source (s) of such higher mortality rates, we made a search into diabetic deaths at our insti-

Ouring the period 1979 through 1983 there were 37 deaths from diabetic coma at our institution, case # declining from 60 per 10,000 admissions (1979) to 30 in 1983. Our average mortality for come for the past 15 yeers is 12.7%, without recent changes. Pediatric admissions for type I, IOOM do not show a secular rise, nor increase in morta-Thus, it appears that such increasing mortality is being generated elsewhere, or might be due to different patterns in death certificate reporting. As we are having sig-nificantly lower number of admissions for diabetic coma we must have data from referring sources to determine whether an lineasing number of these cases are being to ated there. Any way, the divergent trend is mortality in comparison with USA is worrisome and puzzling. Further studies are in order so as to ellucidate the possible reasons.

SERIAL PROLACTIN, TESTOSTERONE AND GONODOTROPHIN LEVELS AFTER VERAPAMIL THERAPY IN MILD TO MODERATE ESSENTIAL HYPERTENSION Francisco García-Cortés, M.D. Juan M. Aranda, M.D., Dilia Díaz, M.D., Carmen Pedrosa, B.S., Zulma Matos, B.S. and Francisco Aguiló, M.D. (Member), VA Hospital and University of P.R. School of Medicine, San Juan, Puerto Rico.

Hyperprolactinemia has been reported after Verapamil (V) therapy. However, prospective studies regarding serial serum prolactin (Pr) changes after V have not been published. Therefore, a six week research protocol was designed to evaluate the short term effects of oral V (240-580 mg/day) in serum Pr, Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH) and Testosterone (T) levels in 12 male patients with sitting diastolic blood pressure (SDBP) ≥95 and ≤114 mm Hg, determined from 3 consecutive readings after a 3 week run in phase. The dosage of V was titrated weekly for 3 weeks (W) if the SDBP remained ≥90 mm Hg. Serum Pr, FSH, LH and T were determined in duplicate samples before and after 3 W of therapy. Two subgroups of pts. were identified. Group A consisted of 6 pts. with a decrease in serum T after 3 W of V therapy (4.9±1.3 to 3.1±.9 MIU/cc, p<.05). Mean serum Pr level significantly increased in this subgroup (5.3±2.1 to 12.9± 3.6 ng/cc, p<.005). There were no statistical significant differences in mean FSH and LH before and after V. Group B consisted of 6 pts. whose T levels remained unchanged or increased (3.9±1.4 to 4.1±1.4 ng/cc, p>.05). Although the mean serum Pr level increased after V, (6.5±3.9 to 11.8±7.9), the difference did not reach statistical significance (p>.05). Mean FSH and LH serum levels remained unchanged. Oral V produces a significant decrease in serum T level in a subset of pts. with arterial hypertension. The decrease in serum T appears to correlate with a statistical significant increase in Pr level.

THE USE OF SUBLINGUAL ISOSURBIDE DINITRATE IN THE TREATMENT OF SEVERLY UNCONTROLLED HYPERTENSION. Fontanet, Hector L., MD (Associate), Garcia, Juan C., MD (Associate), Del Rio, Juan, MD. University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

The blood lowering effects of nitrates are well documented. However, they have not been used previously for the acute control of severe arterial hypertension on asymptomatic patients. In this study a long acting nitrate, Isosorbide Dinitrate (ISDN), was administered sublingually and compared to placebo in a double blind, randomized fashion to determine its effectiveness and safety in the rapid control of severe arterial hypertension. Eleven patients received 10 mg of ISDN with a drop in BP from 205+'8/131 + 3 (mean systolic BP + SE/mean diastolic BP + SE) TO 166+ 9/106 + 5 AT 120 Mins. (P VALUE <0.005). Eight patients received placebo with a drop in BP from 203 + 8/130 + 3 mmHg to 193 \pm 11/122 \pm 5 (P value = 0.5 $\overline{0}$:NS) at 120 mins. When 10 mg. of ISDN was administered sublingually after 120 mins. to placebo pre-treated patients their BP dropped to 161 + 7/105 + 6 (P value <0.005) at 240 mins. our study group (19 patients) was compared to a control group (6 patients) treated only with standard antihypertensive medications and bed rest without Isordil. 5/6 (83%) of the control group achieved steady blood pressure control at 24 hrs. Vs. 9/19 (47%) of the study group pretreated with ISDN (P value = .10: NS). No hypotension, or thostatism, reflex tachycardia or any other side effect were noted on the ISDN treatment group. It is concluded that sublingual ISDN. Safely and effectively lowers sytolic and diastolic BP in patients with severely uncontrolled arterial hypertension.

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SERUM IONIZED CALCIUM (SIC) IN ESSENTIAL HYPERTEN-SION BEFORE AND AFTER THIAZIDE THERAPY. Alfredo Fiallo, MD (Associate) and José L. Cangiano, MD Department of Medicine, Veterans Administration Center, San Juan, Puerto Rico.

Previous studies have shown that hypertensive patients when compared with normotensive controls had a small but significant reduction in SIC. Since chronic administration of thiazide diuretics raises serum calcium, we have measured SIC before and after the administration of Hydrochlorothiazide for four weeks to determine if an increase in SIC is one of the mechanisms by which thiazides reduce blood pressure.

Six male patients with mild to moderate uncomplicated hypertension were studied before and after four weeks on Hydrochlorothiazide 50 mg orally every day for four weeks.

As a group there was no significant (p>0.1) difference in SIC before and after thiazide treatment. Two subgroups of patients could be identified based on the initial Plasma Renin Activity (PRA). Patients with low PRA responded with lowering of mean blood pressure (MBP) and elevation of SIC. Normal or high PRA patients did not respond to therapy with lowering of MBP and did not show an increase in SIC. Volume contraction did not appear to influence blood pressure since there were no alterations in total protein nor hematocrit levels.

In summary, elevation of SIC in low PRA hypertensives is an important mechanism by which thiazide diuretics reduce blood pressure. POSSIBLE ROLE OF ANGIOTENSIN CONVERTING ENZYME (ACE) IN NORMAL RENIN ESSENTIAL HYPERTENSION.

Samuel M. Aguayo, MD (Associate), Julio Benabe, MD.

University of Puerto Rico, San Juan, Puerto Rico.

Essential hypertension is commonly associated with normal plasma renin activity (PRA). The pathophysiology of hypertension in this group is unclear. The ACE is responsible for the degradation of kinins (vasodilators) and the formation of Angiotensin II (vasoconstrictor). We performed the following study to assess the role of ACE in normal renin essential hypertension. PRA and serum ACE activity were measured in 13 ambulatory patients with hypertension after one week free of medications. No significant correlation was found between PRA and serum ACE activity (r=0.05, p>0.1). Five patients were hospitalized for evaluation while on a 70 MEqNaCl diet without medications. After a single dose of the ACE inhibitor captopril (25 mg PO), all of them had a significant fall in systolic (p<0.05), diastolic (p<0.001) and mean blood pressure (p<0.01). The changes in blood pressures were not associated with significant changes in PRA or heart rate but serum ACE activity decreased by 58% (p<0.01). This findings are consistent with a possible role of ACE in normal renin essential hypertension probably mediated through increased kinins degradation. We propose that decreased kinins degradation is the most likely explanation to the acute effects of serum ACE inhibition in patients with normal renin hypertension. 20

SUBLINGUAL NIFEDIPINE IN HYPERTENSIVE EMERGENCIES

José Váz quez Tanus, M. D. (Associate) César Trabanco, M. D. (Associate), Julia Torres, M. D., (Associate), Orlando Marini, M.D., (Associate), Miquel Pérez Arzola, M.D., FACP

Institution : Damas Hospital

Purpose : To evaluate the efficiency and safety of sublingual nifedipine in controlling hypertensive emergencies as first line drug.

Methods: Patients with symptomatic diastolic BP elevation of 120mmHg irrespective of etiology, complications or previous treatment, provided the patients had not received antihypertensives during the previous 12 hours. Pateints were given 10 mg. nifedipine sublingually at five minute interval. Recordings of BP and heart rates were made during this time.

: Thirty eight patients were studied including four with acute MI, two in pulmonary edema, and six with a stroke in evolution. Preexisting medical conditions included Diabetes Mellitus (6%) ESRD (6%) SLE (3%) and Essential Hypertension (52%). All had at least a grade III retinopathy. After the first dose, diastolic and systolic BP decreased significantly in all cases as determined by 3-5 minutes interval measurements and persisted over 30-90 minutes. Mean systolic decrease was 41 mmHg at 30 minutes, and mean diastolic 37 mmHg at 30 minutes. Only side effects were unifocal PVC's in one case and dizziness in another. Mean heart rate increased from 84 to 93 but there was not a single case of tachycardia over 100/minute, or serious arrhythmias.

It is concluded that nifedipine sublingually is an effective, simple and safe drug in the management of hypertensive emergencies.

EFFECT OF SUBLINGUAL NIFEDIPINE IN AMBULATORY HYPER-TENSIVE EMERGENCIES Rafael Rodríguez López, M.D. (ACP Associate), Carlos E. Girod, M.D. FACP, and Harry Rosado, M.D. (Associate), University of Puerto Rico, School of Medicine, San Juan, Puerto Rico.

To evaluate the efficacy and safety of sublingual nifedipine to control hypertension rapidly in the ambulatory setting, 13 patients seen in the emergency room or in the internal medicine clinics with diastolic blood pressure (BP) consistently recorded in the 110 mmHg. range or over, were given 10 mg. of sublingual nifedipine. All the patients responded with an average reduction in systolic BP from 209 + 27 mmHg to 150 + 24 mmHg (p=.005); in diastolic BP from 122 + 11 mmHg to 90 + 6 mmHg (p=.005); and with a reduction in mean arterial pressure of 151 + 12 mmHg to 110 + 10 mmHg (p=.005) in average time of 40 mins.

Side effects were minimal and inconsequential. There was no reflex tachycardia or postural

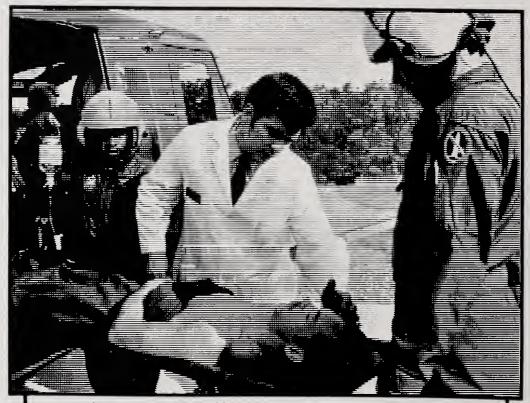
hypotension.

Nifedipine sublingually proved to be a safe and effective therapy for rapid control of hypertension and may be the therapeutic modality of choice in the management of uncontrolled, uncomplicated arterial hypertension in ambulatory patients.

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PHYSICIANS, A WEEKEND WITH THE RESERVE ISN'T JUST ANOTHER DAY AT THE OFFICE.



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HEPATITIS B VACCINE FREE OF HTLV-III

Health care workers who have received hepatitis B vaccine do not appear to have antibodies to HTLV-III, the virus believed to cause AIDS. The finding is reported in JAMA.

Jules L. Dienstag, MD, of Massachusetts General Hospital, and colleagues studied 15-month post-vaccination serum samples from 100 health care workers who had received the vaccine and from 100 who had received placebo injections. None of the 200 employees had serological evidence of HTLV infection.

"These serological findings lend additional support to earlier epidemiologic and immunologic observations suggesting that hepatitis B vaccine does not transmit infection with an AIDS virus," the researchers say. Many health care workers and others at risk of acquiring hepatitis B have been reluctant to receive the vaccine because of a suspected risk of contracting AIDS. The vaccine is prepared from hepatitis B surface antigen purified from plasma of carriers of the antigen, and many of these donors were homosexual men from New York, San Francisco an Los Angeles. The vaccine was introduced in 1982, about the same time AIDS was recognized.

The researchers point out that the real risk of contracting AIDS from such a vaccine is remote. The hepatitis B antigen particles are subjected to a triple step inactivation process that abolishes the infectivity of every known class of viruses. They also note that long-term follow-up of vaccinated and unvaccinated groups of homosexual men has shown no increased risk of AIDS in vaccine recipients.

The plasma used to prepare the vaccine used in this study was collected between 1977 and 1979, the researchers say, noting that this was before AIDS became epidemic in high-risk groups, but that incidence of the syndrome increased dramatically during this period. The number of recipients in this study is too small to exclude any potential risk from the vaccine, the researchers say. "On the other hand, these new findings...provide reassurance that hepatitis B vaccine is safe and does not transmit AIDS."

JAMA August 23, 1985

AIDS VIRUS NOT TRANSMITTED BY MOSQUITOES

No current epidemiologic or microbiologic evidence supports the theory that AIDS is transmitted by mosquitoes, writes D. Peter Drotman, MD, MPH, of the Centers for Disease Control in Atlanta, responding to a question by the *Journal of the American Medical Association*. "The bulk of evidence argues against routes of transmission other than sexual or blood related," he says. "In other countries, such as Haiti or countries in Central Africa, heterosexual transmission seems to play a more important role than in North America or Western Europe (where most AIDS patients are homosexual)." But insect-borne transmission has not been implicated in any country, and the relative absence of reported disease in preadolescent children argues against it, he concludes.

JAMA August 23, 1985

COMBINED THERAPY ENHANCES PANCREATIC CANCER SURVIVAL

Survival was significantly prolonged in a prospective study of pancreatic cancer patients treated with radiation and chemotherapy following surgery, researchers report in the August *Archives of Surgery*. Martin H. Kalser, MD, of the University of Miami, and Susan S. Ellenberg, PhD, of EMMES Corp., in Potomac, Md., say a study of 21 patients assigned to study and 22 to observational control had to be interrupted because combined therapy was so effective. "Median survival for the treatment group (20 months) was significantly longer than that observed for the control group (11 months)," the researchers say.

POLYSORBATE 60 WON'T CURE MALE BALDNESS

Results of a double-blind placebo-controlled trial of polysorbate 60, a nonionic detergent, indicate that the substance is ineffective, despite anecdotal reports of its ability to cure male pattern baldness. Howard D. Groveman, MD, and colleagues from the University of California, San Diego, say 141 subjects completed a 16-week trial and that no measurable differences in new hair growth, which did not correlate with measurements. "The placebo effect may be a major factor in reports of baldness 'cures,' "the researchers comment in the August Archives of Internal Medicine.

ANTIDEPRESSANTS USED TO TREAT HYPERACTIVITY

Monoamine oxidase inhibitors, antidepressant drugs, may be a useful alternative to stimulants in the treatment of selected patients with attention deficit disorder (ADD) and hyperactivity, according to a study in the October *Archives of General Psychiatry*. Alan Zametkin, MD, of the National Institute of Mental Health in Bethesda, MD., and colleagues conducted a double-blind, crossover study with 14 patients (mean age 9.2 years) and found that the antidepressant drugs had "immediate, clinically significant benefit." The immediate response to the drugs indicates a different mechanism in ADD patients from that mediating the antidepresant effect associated with typical use of the drugs.

LANGUAGE RECOVERY MORE RAPID AFTER STROKE

Language deficits are reduced more rapidly and more completely than are congnitive deficits in patients with subcortical stroke, according to a study in the October Archives of Neurology. Davida Fromm, MS, of the Western Psychiatric Institute and Clinic in Pittsburgh, and colleagues prospectively and systematically studied 16 patients, noting patterns of lesion and impairment. "Recovery was most dramatic within the first six to eight weeks after onset," they say.

UNIQUE LYMPHOMA MARKS EXPOSURE TO HTLV-III

Malignant lymphoma among homosexual men has unique characteristics that may help to define cases related to the current AIDS epidemic. Median survival, despite treatment, for 27 patients so defined was eight months, according to a report in JAMA.

Alexandra M. Levine, MD, of the University of Southern California School of Medicine, and colleagues report that the sites and accompanying symptoms of malignant lymphoma found in 27 homosexual men differed markedly from characteristics of the same disease in 11 heterosexual patients.

"Of the homosexual lymphoma patients, 85 percent presented with disease in extranodal sites (other than the lymph nodes), including the central nervous system and rectum, and 81 percent had reversed T-helper/suppressor ratios," the reseachers say. Twenty of these patients were tested for HTLV-III antibody; 13 of 15 (87 percent) with high-grade lymphoma and two of five (40 percent) with low-grade disease were antibody-positive.

The disease is usually confined to the lymph nodes, the researchers point out. Among the 11 heterosexuals with high-grade lymphoma, only four (36 percent) had extranodal disease, with central nervous system involve-

ment present in one (9 percent). Only one of the heterosexual patients had antibody to HTLV-III.

"Malignant lymphomas occurring in homosexual men are distinctive, both pathologically and clinically, when compared with prior series of non-Hodgkin's lymphoma or to the current heterosexual lymphoma cases diagnosed during the same period," the researchers say.

"The acquired immunodeficiency syndrome-related lymphomas in homosexual men are extranodal, high-grade, B-lymphoid tumors, associated with exposure to HTLV-III and unusual clinical characteristics," the researchers conclude. Optimal treatment for these patients has not been found, they add. Most of their homosexual patients have died as a result of underlying lymphoma, despite intensive multiagent chemotherapy. Median survival time was eight months. They suggest that attention to the nervous system may be important early in the course of the disease, since this site may foster relapse or diasease progression despite high doses of methotrexate.

JAMA October 11, 1985

BLOOD PRESSURE CONTROLLED BEST THROUGH FREE CARE

High blood pressure is reduced and controlled more effectively in patients with access to free medical care than in patients required to pay at least part of charges for services, according to a comprehensive study from the Rand Corporation that appears in JAMA.

Emmett B. Keeler, PhD, of the Santa Monica, California research organization, and colleagues studied how cost sharing through various health insurance programs affected the actions of hypertensive patients and their physicians. Their study, which ran from Novemeber 1974 through January 1982, included 3,958 adults; 856 of whom were hypertensive. Seventy percent of the subjects remained in the study for three years and 30 percent for five years. Fourteen insurance plans were grouped into four categories: three involving cost sharing and one providing free coverage for all services.

Blood pressure were significantly lower by the end of the study for subjects receiving free care, the researchers report, noting that this difference was even more pronounced in low-income hypertensives. "Differences of 1.9 mm Hg in diastolic blood pressure... or of 3.5 mm Hg in the low-income hypertensives are important—they translate into differences of 5 percent to 8 percent in the probability of dying in the next year," they point out.

"The cause of the difference was the additional contact with physicians under free care," the researchers say. "This led to better detection and treatment of hypertensives not under care at the start of the study." Recipients of free care were also more likely to follow recommendations regarding diet and smoking, and to obtain and use appropriate medication.

Among subjects on cost sharing plans, the researchers found that initial screening for high blood pressure led to lower average blood pressure at the end of the study. AMA News 1 of 77 \unit 11

"For the cost-sharing plans, the examination plus notifications may have substituted for the additional contact induced by free care," they observe. But compliance with many quality-of-care criteria was low, even for those on the free plan, and many subjects still had uncontrolled blood pressure or anxiety about their blood pressure. The researchers conclude, "If the cost of care had been the main problem in hypertension control, the free plan would have scored higher and the differences between the plans would have been larger."

JAMA October 11, 1985

ELEVATED WHITE BLOOD CELLS LINKED TO CORONARY RISK

The risk of coronary heart disease death decreases 14 percent for each decrease of 1,000 white blood cells per cubic millimeter of blood, according to a study reported in JAMA. "The white blood cell count was also significantly associated with cancer death," and researchers from the National Heart, Lung and Blood Institute group reporting the finding.

"Total white blood cell (WBC) count was found to be strongly and significantly related to risk of coronary heart disease (CHD), independent of smoking status," say Richard H. Grimm, Jr., MD, and colleagues, commenting on a study of 6,222 middle-aged men included in the Multiple Risk Factor Intervention Trial Research project. "Change in WBC count from baseline to the annual examination just prior to the CHD event was found to be a significant and indenpendent predictor of CHD risk," they add.

Smoking was strongly related to white blood cell count. "Smokers on average had a WBC count of 7,750/cu mm compared with 6,080/cu mm for non-smokers," the researchers say.

Whether elevated white blood cell count is a cause or a consequence of disease remains to to established, the researchers comment. "The WBC count could represent a highly sensitive measure of early disease, or could be elevated by toxic substances found in cigarettes, the elevated cell count representing a better indiator of toxic exposure than either reported cigarette consumption or serum thiocyanate level (a standard measure).

"We cannot determine from these data whether WBC count is a cause or consequence of the disease process in this high-risk male population; nevertheless, WBC count is a potent independent predictor of future CHD and cancer," they say. "The measurement of total WBC count and specific cell types may prove a significant addition to risk assessment.

"Change in WBC count may also be a useful clinical index to gauge change in coronary heart disease risk while validating self-reported change in smoking."

JAMA October 11, 1985

NEW STRATEGIES OFFERED TO CURTAIL AIDS EPIDEMIC

With documented evidence that the AIDS virus now is spreading to heterosexuals, researchers are offering new strategies to contain the infectious agent that destroys the body's immune system. The suggestions are based on new studies reported in JAMA that confirm the spread of AIDS both to heterosexuals and to three hospital workers, one of whom apparently infected her sexual partner even though she did not show presence of AIDS antibodies.

In an editorial comment, Dean F. Echenberg, MD, PhD, recommends tracing all heterosexuals though to have been exposed to the AlDS retrovirus. This is possible, he asserts, because the prevalence of infection among heterosexuals still is less than 1 percent. "We know that AlDS is spreading within the heterosexual population. The only question is how fast and how widely," he says.

Echenberg doubts that a mass education campaign will curb the spread of AIDS among heterosexuals, despite the effectiveness of such campaigns among homosexual men in San Francisco. "The immediacy of AIDS that has driven changing sexual practices in the San Francisco gay community is lacking" in the much larger and more diverse heterosexual population, he notes.

Between 40 and 60 percent of homosexual men in San Francisco are now infected with the AIDS virus. Since the virus already has appeared in the heterosexual population, the AIDS epidemic clearly will not be limited to high-risk groups, Echenberg warns. The problem of containing the virus is linked to its long incubation time. "Since AIDS has an incubation period of up to five years, asymptomatic infected heterosexuals may be unknowingly spreading (the virus) to their sexual contacts," he says. Hence the need for rigorous tracking of individuals possibly exposed to the virus. Infection with the virus is determined by presence of antibody to the virus in a person's blood.

Echenberg's comments accompany a new study from the Walter Reed Army Institute of Research in Washington, D.C. Robert R. Redfield, MD, and colleagues recently evaluated 41 patients with AIDS, and found that 15 of these patients (37 percent) acquired the infection from a sexual partner(s) of the opposite sex. "Heterosexual contact with partners who developed AIDS or who were at risk for AIDS was confirmed in six patients," they report. "The remaining nine patients had multiple (more than 50) heterosexual partners and/or sexual contact with prostitutes." The researchers add that the type of sexual activity did not appear to be related to disease acquisition, but that receptive anal intercourse was definitely not implicated.

"The epidemiology of HTLV-III disease resembles that of hepatitis B virus, an agent clearly heterosexually transmissible," Redfield and colleagues say. They add that it is not clear how the virus is transmitted from women to men; the virus has been isolated from semen and saliva, but has not yet been reported to be found in

vaginal excretions.

Another major study describes three cases of AIDS virus infection in hospital workers who accidentally punctured their hands with needles used on patient with AIDS. Stanley H. Weiss, MD, of the National Cancer Institute, and colleagues report that although one of these workers did not show presence of antibody, she apparently transmitted the virus to her sexual partner. The other two workers (and one worker's sexual partner) are antibody-positive. Of 39 total workers who reported possible exposure through such injuries, no other cases of infection were noted.

"The risk of nosocomial HTLV-III transmission appears to be low and related to percutaneous exposure," the researchers conclude. They add that systematic training in the handling of phlebotomy instruments should reduce the risk of occupational exposure.

Difficulties remain in collecting and interpreting data from persons thought to be at risk for AIDS. Commenting on the Weiss study, Lawrence D. Grouse, MD, PhD, observes, "It is impossible for a study to come to valid conclusions about transmission of HTLV-III infection without complete knowledge of patient risk factors. It is unlikely that such documentation would be possible without the guarantee of complete confidentiality that was provided in this study."

In the Letters section, Michael Marmor, PhD, of New York University Medical Center, and colleagues stress the need for better educational efforts for drug abusers. They note that more than 50 percent of this high-risk group in New York City may be infected with the virus. They also point out that many prostitutes are IV drug users, which increases their chances of infectivity.

In another letter, Neil Schram, MD, Past President of the American Association of Physicians for Human Rights, San Francisco, says physicians should educate their patients that everyone who is not in a mutually monogamous relationship is at some risk of acquiring AIDS, but adds that it is unreasonable to expect celibacy for those who are infected or monogamy for those not infected. Schram also calls for more study of the possible transmission of the virus through kissing.

JAMA October 18, 1985

FURTHER EVALUATION OF HEPARIN FOR STROKES NEEDED

Further evaluation of the use of heparin following transient ischemic attacks (TIAs) to prevent cerebral infarction is called for, according to a report in the October Archives of Neurology. Heparin, which prevents clotting of blood, has been used following TIAs since the 1940s, but in a study of 74 patients Steven F. Putman, MD, and Harold P. Adams, Jr., MD, of the University of Iowa Hospitals in Iowa City, found that 12 patients had recurrent TIAs and five had cerebral infarction during treatment. In addition, nine patients had bleeding complications. "Further evaluation of heparin therapy is appropiate," they say, pointing out that the only other

therapeutic option now available would be use of antiplatelet-aggregating agents, whose value also is not known.

EARLY PREGNANCY LINKED TO HEIGHT, EARLY MATURATION

A survey of 1,844 lower income women shows a significantly earlier onset of puberty for adolescents (12 to 16 years) experiencing their first pregnancy compared with adults (17 to 31 years), according to a report in the October American Journal of Disease of Children. In addition, the adolescent mother-to-be were taller and heavier (prepregnancy) than National Center for Health Statistics standards and had a significantly greater weight-for-height, report Charles Hoff, PhD, and colleagues from the University of South Alabama Medical Center in Mobile. "These comparative findings have relevance both to the maturational status of the Mobile patients and to the impact of government public assistance on the health and well-being of these patients," they say.

DEFINE A PHOTODERMATITIS AFFECTING HAWAII TOURISTS

"Papulovesicular light eruption" is offered as a name to describe a distinct condition that commonly affects young to middle-aged white women visiting Hawaii by researchers from Kauai. Reporting in the October Archives of Dermatology, David J. Elpern, MD, of the Kauai Medical Group, and colleagues say they analyzed 150 cases papulovesicular eruptions (small solid or fluid elevations of the skin) affecting female visitors to the Pacific islands. "The majority (83 percent) of patients resided in the more northerly mainland states and Canada," they point out, adding that most eruptions followed exposure to sunlight and are confined to exposed areas of the body.

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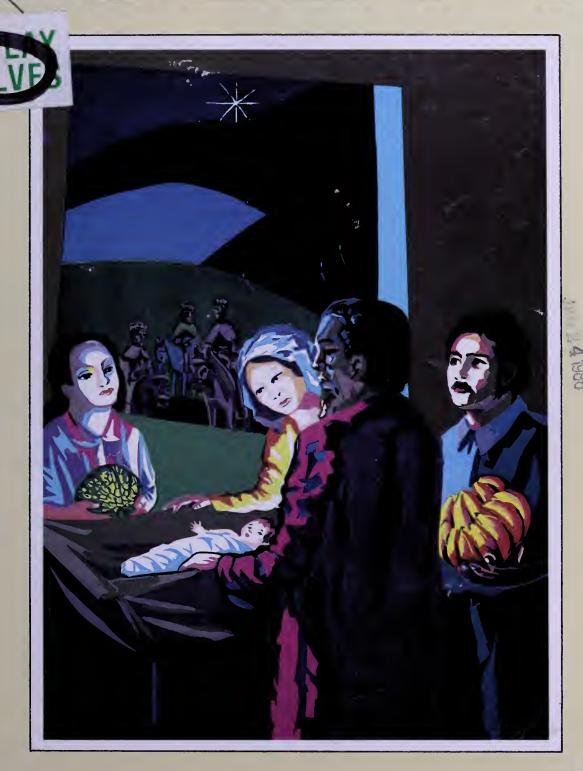
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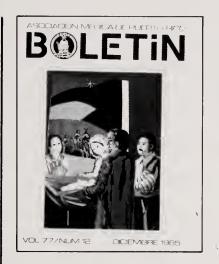
on este número se completa el volumen 77 del Boletín y el cuarto año de la actual Junta Editora. Durante este año se ha logrado continuar la política editorial de artículos de calidad científica y valor práctico resaltando sobre todo la experiencia local. La revista continuó circulando con puntualidad y por segundo año consecutivo dejó beneficios económicos considerables a la Asociación Médica de Puerto Rico. Se aumentó su circulación por 300 ejemplares mensuales y se le envió libre de costo a los Internos y Residentes de la Escuela de Medicina de la Universidad de Puerto Rico y el Hospital Regional de Caguas.

Se nos ha encomendado la tarea de continuar en nuestros puestos durante el 1986 y nuestros objetivos son sencillamente mantener los standards científicos y gráficos hasta ahora alcanzados. Confiamos también obtener los recursos para lograr aumentar la circulación mensual por 500 números de manera que la difusión del Boletín tenga mayor alcance.

La Junta Editora quiere aprovechar para desearle a todos nuestros lectores muchas felicidades en esta época navideña. Para el 1986 les deseamos mucha salud y mejores intenciones.

Kiranimi Ino

Rafael Villavicencio, MD, FACC Presidente Junta Editora Boletín Asociación Médica de Puerto Rico



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NUESTRA PORTADA

Cartel Navideño por el artista puertorriqueño Antonio (Tony) Maldonado. Este cartel fue hecho para anunciar el programa de la Navidad de 1982 que auspiciaba la división de Educación a la Comunidad del Departamento de Instrucción Pública.

Tony nació en el sector de Palo Alto del barrio Coto Sur de Manatí en el año 1920. De muy niño su aficción por el dibujo era grande, copiaba todo lo que caía en sus manos, fotos de periódicos, ilustraciones de libros, estampas religiosas, etc. Mientras cursaba el sexto grado en la Escuela José Severo Quiñones su maestra de español, doña Magda López de Victoria, vista su aficción por el dibujo, lo incluyó en las clases de dibujo que daba en su casa luego de las horas escolares. Al terminar el curso de arte fue galardonado con el primer premio de la clase, consistente en una caja de pinturas de agua con las que se inició en la brega del color.

En 1936 ingresa al taller del maestro Juan A. Rosado en Puerta de Tierra, donde estudia dibujo por algún tiempo. Por varios años permanecerá aquí pintando rótulos, mientras hace sus estudios de Escuela Superior en la Escuela Nocturna Labra. Sigue las prácticas del dibujo con el maestro Sánchez Felipe, de pintura con Gretchen Wood y en la Universidad de Puerto Rico asiste como oyente a las clases de dibujo y pintura de don Cristóbal Ruiz. Marcha en el 1947 a Méjico para ingresar en la Escuela Nacional de Artes Plásticas donde permanece por tres años

De nuevo en Puerto Rico trabaja por algunos años en el taller del maestro Rosado. En Manatí labora por algún tiempo como escultor en la fábrica de figuras para Nacimientos Miller. En los inicios de la televisión en Puerto Rico laboró como escenógrafo en Telemundo. En 1957 trabaja en el taller de artes gráficas de la División de Educación de la Comunidad, donde aun permanece.

Desde sus inicios como pintor su predilección por la acuarela es manifiesta. Tal vez por las propiedades de este medio para fijar la atmósfera cambiante del paisaje de nuestra tierra. También ha hecho trabajos al temple y al óleo, varios retratos, algunos murales, grabados, etc. En la División ha realizado numerosas ilustraciones para libros, e infinidad de carteles para películas y actividades del programa, así como para otras agencias y entidades interesadas. También ha realizado escenografias para el teatro Tapia y otros teatros del país.

Su primera exposición fue precisamente de acuarelas en el 1941 en el Ateneo Puertorriqueño y desde entonces su obra ha figurado en numerosas exposiciones colectivas en nuestro país y el exterior.

La reproducción de la obra en nuestra portada ha sido posible gracias a la cooperación del autor con nuestra Asociación. Le damos las gracias a Tony Maldonado.



BOLETIN DE LA ASOCIACION MEDICA PUERTO RICO

AGRADECIMIENTO A COLABORADORES

La Junta Editora del Boletín de la Asociación Médica de Puerto Rico quiere al finalizar este año testimoniar su agradecimiento a una serie de personas que nos brindaron en todo momento su valiosa cooperación y desinteresada ayuda.

Algunos realizaron la difícil labor de evaluar los trabajos para publicación, otros proveyendo asesoramiento y algunos supliendo material gráfico y científico de interés.

El Boletín ha tenido un año exitoso, las metas propuestas fueron alcanzadas y superadas; nuestra revista dejó beneficios a la Asociación Médica por primera vez en su historia; recibimos felicitaciones nacionales y del exterior y sobretodo nuestra matrícula ha manifestado su agrado unánime. La ayuda de estas personas permitió esto se lograse. A todas ellas nuestras mas sinceras gracias y profundo agradecimiento.

Dr. Juan Aranda

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7 y NJ 12

WALLACE LABORATORIES Division of Carter-Wallace, Inc. Cranbury, New Jersey 08512

Please see the following page for a prief summary of prescribing information.

TUSSI-ORGANIDIN® with Codeine TUSSI-ORGANIDIN® DM

Before prescribing, please consult complete product information, a brief summary of which follows:

Indications and Usage: For the symptomatic relief of irritating, nonproductive cough associated with respiratory tract conditions such as chronic bronchits, bronchial asthma, tracheobronchitis, and the common cold, also for the symptomatic relief of cough accompanying other respiratory tract conditions such as laryngitis, pharyngitis, croup, pertussis and emphysema. Appropriate therapy should be provided for the primary disease.

Contraindications: History of marked sensitivity to inorganic iodides, hypersensitivity to any of the ingredients or related compounds, pregnancy, newborns, and nursing mothers

Warnings: Discontinue use if rash or other evidence of hypersensitivity appears. Use with caution or avoid use in patients with history or evidence of thyroid disease.

Precautions: General—lodides have been reported to cause a flare-up of adolescent acne. Children with cystic fibrosis appear to have an exaggerated susceptibility to the gotrogenic effects of iodides.

Dermatitis and other reversible manifestations of iodism have been reported with chronic use of inorganic iodides. Keep these in mind in patients receiving these preparations for prolonged periods.

Drug Interactions—lodides may potentiate the hypothyroid effect of lithium and other antithyroid drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No long-term animal studies have been performed.

Pregnancy—Teratogenic effects: Pregnancy Category X (see CONTRAINDICATIONS).

Nursing Mothers -- Do not administer to a nursing woman

Adverse Reactions: Side effects have been rare, including those which may occur with the individual ingredients and which may be modified as a result of their combination. Organidin—Gastrointestinal irritation, rash, hypersensitivity, thyroid gland enlargement, and acute parotitis. Codeine—(Tussi-Organidin only): Nausea, vomiting, constipation, drowsiness, dizziness, and miosis. Dextromethorphan—(Tussi-Organidin DM only): Drowsiness or gastrointestinal disturbances.

Drug Abuse and **Dependence** (Tussi-Organidin only): Controlled Substance—Schedule V. Dependence—Codeine may be habit-forming.

Overdosage: No reports of any serious problems.

Dosage and **Administration**: Adults: 1 to 2 teaspoonfuls every 4 hours.

Children: 1/2 to 1 teaspoonful every 4 hours.

How Supplied: *Tussi-Organidin Liquid*—clear red liquid, in bottles of one pint (NDC 0037-4812-10) and one gallon (NDC 0037-4812-20).

Tussi-Organidin DM Liquid—clear yellow liquid, in bottles of one pint (NDC 0037-4712-10) and one gallon (NDC 0037-4712-20).

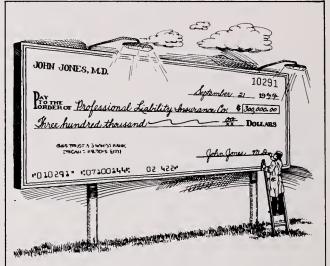
Storage: Store at room temperature, avoid excessive heat. Keep bottle tightly closed.

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Rev. 4/84





A Sign of the Times?

n 1983, 22 physician-owned professional liability insurance companies were forced to raise their premiums an average of 17 percent. At that rate, highrisk insurance coverage that cost \$63,000 in 1983 could top \$300,000 in just ten years.

These costs are leading to an affordability crisis which affects everyone. Physicians are concerned about rising premiums, exorbitant awards and continued insurance availability. Patients pay the price in increased costs and limited access to care.

Liability problems exact a high toll on physicians—in time and money, and even on their health. Some have been forced into early retirement; others have modified their practices to avoid highrisk procedures.

There is help. The American Medical Association's Special Task Force on Professional Liability and Insurance has developed an ambitious plan of action to respond to the crisis. This includes reviewing tort reform, working with the nation's policymakers to address the issue, promoting state coalitions to deal with the problem, distributing patient information materials and instructing physicians on how to avoid lawsuits.

If you want something done about the professional liability problem, become part of the solution: join the AMA.

For information, call toll-free 800/621-8335 (in Illinois, call collect 312/645-4783), or write:

The American Medical Association

Division of Membership 535 North Dearborn Chicago, Illinois 60610

ESTUDIOS CLINICOS

Skin Cancer in Puerto Rico

Aida L. Quintero, MS IV Sheila M. Torres, M.D. Jorge L. Sánchez, M.D.

Abstract: The incidence of cutaneous cancer in Puerto Rico in 1981 was studied and compared with its incidence in 1974, showing a statistically significant increase. Most of the cancers were basal cell carcinoma with no significant differences between the two sexes, but showing an increased incidence with increasing age. As expected, most of the lesions were located on sun-exposed areas of the skin.

utaneous cancer represents the most frequent cancer in the island of Puerto Rico. They were included in the statistics of the Puerto Rico Cancer Registry until 1974 when their registry was discontinued. Malignant melanoma still continues to be included in the statistics. At that time, skin cancer constituted approximately 20.2% of all cancers registered at the center. It is the purpose of this study to retrospectively determine the incidence of cutaneous cancer including basal cell carcinoma (bcc), squamous cell carcinoma (scc), and malignant melanoma (mm) in Puerto Rico during 1981, and compare our data with the data at the Puerto Rico Cancer Registry in 1974.

Materials and Methods

Twenty six pathology departments and private laboratories which included the hospitals of most major cities and all major teaching hospitals were included in the study. The Oncologic Hospitals in San Juan and Ponce, the Department of Dermatology of the University of Puerto Rico School of Medicine and the Pathology Department of the Puerto Rico Medical Center contributed most of the material.

The pathology reports from those laboratories from January 1981 to December 1981 were revised for the histological type of skin cancer (bcc, scc, mm), age and sex of the patient as well as location of the lesion.

Excluded from the study were cases of recurrent malignancy and carcinoma in situ. Multiple skin cancers

for a given patient were accepted only if these were histologically different. Reports of basosquamous carcinoma were codified under basal cell carcinoma. Tissue samples which were referred to the Oncologic Hospital in San Juan were excluded if they had already been counted at the refering institution.

All the data was codified, stored and analized with the assistance of Dr. Rafael Rivera Castaño and the computer system at the School of Public Health of the University of Puerto Rico, Medical Sciences Campus.

All statistical analysis was carried-out using the Chi-Square Test.

Results

In 1981, a total of 6086 malignancies, excluding cutaneous cancers, were registered at the Cancer Registry.² We found a total of 1717 cutaneous cancers (bcc, scc, and mm) from the files of those hospitals and pathology laboratories which were visited. This number represents 22% of total cancers reported to the Cancer Registry of P.R. in 1981.

Of the 1717 cancers, there were 1343 bcc, 326 scc, and 48 mm. There were 863 carcinomas in males and 849 in females representing, respectively, 21.4 and 22.6 percent of the total cancers in each sex in 1981. (See Table I) The sex was not specified in 5 of them. When dividing them by sex, there were 653 males and 686 females with bcc; 176 males and 150 females with scc; and 34 males and 13 females with mm, the latter having a ratio of 2.6 males to females which is statistically significant. (See Table I)

TABLE I

Incidence of Cutaneous Carcinomas						
CA Type/Sex	Basal cell	Sq. Cell	Melanoma	Total		
Male	653	176	34	863		
Female	686	150	13	849		
Total	1339	326	47	1712		

^{*}Age was not given in 5 cases.

Table II illustrates the following points with respect to the incidence of cutaneous carcinomas by age and sex: the number of cutaneous carcinomas increases with increasing age; the age bracket in which the incidence is

From the Department of Dermatology, Medical Sciences Campus, School of Medicine, University of Puerto Rico

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highest is the 7th decade followed by the 8th and 6th, there being no significant difference between males and females in these age groups. The three types of cutaneous cancers individually followed the same trend. In the 31 to 40 years of age group, there are 24 males and 43 females, which is statistically significant. (See Table II) It is important to note that there are 234 cases where no age was given.

In both sexes, the most frequent location was the head and neck. (Table III) Except for the trunk, in which the male/female ratio was 1.4 there were no statistically significant differences between the two sexes.

TABLE II

Incidence of Cutaneous Carcinoma by Age and Sex					
Ages (Yrs)	Male	Female	Total		
11 - 20	2	0	2		
21 - 30	8	14	22		
31 - 40	24	43	67		
41 - 50	73	63	136		
51 - 60	141	149	290		
61 - 70	198	195	393		
71 - 80	790	175	365		
81	85	123	208		
_Total	721	762	1483		

Cutaneous cancers are thought to be related to sun exposure among other variables. Most of our cases occured on the head and neck. An observation which may be related to working habits is that there is a statistically significant greater incidence of cancer on the trunks of males. However other studies have found a greater incidence of cutaneous cancer on the lower extremities of females relating this to greater actinic exposure. In our study this was not the case, in fact, in the lower extremities males had more cancers than females, but this was not statistically significant.

In sum, it is evident that there is an increase in the incidence of cutaneous carcinomas when we compare the data of 1974 with the data of 1981. The incidence in 1974 per 1000 habitants was 0.415 and in 1981 it was 0.525. This difference is not statistically significant. When we consider the fact that we have probably missed a considerable number of cases from private laboratories and hospitals, the latter incidence is probably higher.

TABLE III

Localization of Skin Cancer							
Localization	Head & Neck	Trunk	Upper Ext.	Genitalia	Lower Ext	Unknown	Total
Male	653	56	52	12	24	66	863
Female	653	39	42	18	17	80	849
Total	1306	95	94	30	41	146	1712

Discussion

In general terms, our study substantiates the findings of previous studies on the incidence of cancer in the United States^{3, 4} and Latin America.⁵ Cutaneous cancer was the most frequent cancer in Puerto Rico in 1981. The incidence is estimated at 0.525/1000 habitants compared to 0.36/1000 female habitants for breast cancer and 0.39/1000 males habitants for prostate cancer.² These two types of cancer are listed as the most frequent noncutaneous ones at the Cancer Registry.²

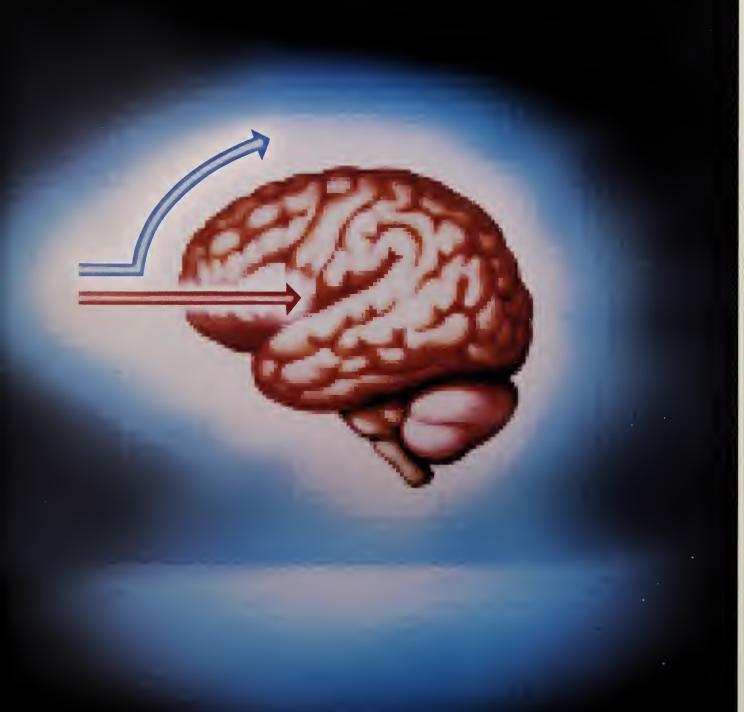
Clinical experience shows us that cutaneous cancer, particularly bcc and scc, occur primarily in the elderly. This impression is corroborated by the fact that 73% of the cases occur in patients age 50 or above and 65% occur in patients age 60 or above.

There was no difference between the sexes in the incidence of cutaneous cancers in the different age brackets except for the 31 to 40 years group in which there was a female/male ratio of 1.8. These statistics may not be representative because of the 234 cases in which the age was unknown, 60% were males.

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The hydrophilic advantage in hypertension...



The hydrophilic advantage.

Highly hydrophilic TENORMIN* (atenobal)

...does not readily cross the blood-brain barrier.

...associated with few CNS side effects.

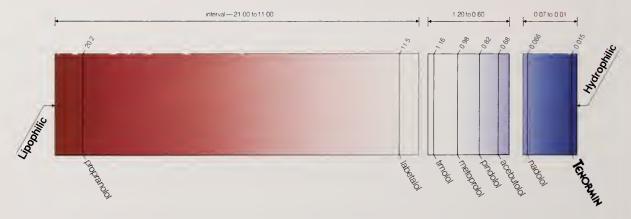
At therapeutic dose levels, hydrophilic TENORMIN has brain concentrations about 20 times lower than those of lipophilic propranolol and about 10 times lower than those of metoprolol.¹

Hydrophilic

Lipophilic

TENORMIN is associated with a lower incidence of CNS side effects (including sleep disturbances, fatigue, and depression) than are the lipophilic agents.¹⁻⁶

Relative Hydrophilicity/Lipophilicity of Currently Available Beta Blockers (distribution coefficients *n*-octanol/buffer at pH 7.4 and 37°C)²



Clinical study on sleep: **TENORMIN** superior to lipophilic agents.

In a clinical study (n=10) comparing the effects on sleep of TENORMIN, propranolol, metoprolol, and pindolol, hydrophilic TENORMIN proved superior to the lipophilic agents in minimizing an abnormal number of dreams, nighttime awakenings, and early-morning awakenings.³

Other studies show improved quality of life when patients switched to hydrophilic TENORMIN.

In a group of 720 patients treated with lipophilic beta blockers, 23% (167) discontinued therapy because of side effects. Of these, 37% (62) were related to the CNS.

When switched to TENORMIN, 93.5% (58) of these patients had CNS symptoms which disappeared or markedly improved.⁷

See following page for brief summary of prescribing information.





The hydrophilic advantage...for virtually all your hypertensive patients.

TENORMIN® (atenolol)

A beta, selective blocking agent for hypertension.

DESCRIPTION: TENORMIN (atenolol), a synthetic, beta, selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4 [2'-hydroxy-3'-[(1 methylethyl) amino) propoxy). Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 265 mg/mL at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCI (300 mg/mL at 25°C) and less soluble in chloroform

INDICATIONS AND USAGE: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than tirst degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractifity and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously Both digitalis and atenoid slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN therapy should be withdrawn.

IEND/MMIN therapy should be withdrawn. Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice Even in the absence of overt angina pectoris, when discontinuation of TENORMIN is planned, the patient should be carefully observed and should be advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

advised to limit physical activity to a minimum. TENORMIN should be reinstated if withdrawal symptoms occur.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a beta; stimulating agent (bronchodilator) made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels. Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium such as ether. Cyclopropane, and trichloroethylene.

last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium such as ether, cyclopropane, and trichloroethylding. TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg. dobutamine or isoproterenol with caution—see OVERDOSAGE). Manifestations of excessive vagal tone (eg. profound bradycardia, hypotension) may be corrected with atropine (1-2 mg/lV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta adrenergic blockade may mask certain clinical signs (eg. tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm, therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely.

should be monitored closely

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Catecholamine-depleting drugs (eg. reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long iterm (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various

mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at at tested dose levels of atenolol (starting at 15 mg/kg/day or 75 times the maximum recommended human dose) and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively). USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN (atenolo) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

worrien. It is Unit with a tenoion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not established to what extent this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving atenoiol. Pediatric Use: Safety and effectiveness in children have not been established ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patien. (Us studies) or elicited, e.g. by checklist (foreign studies) The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the US studies (volunteered side effects) and then from both US and foreign studies (volunteered and elicited side effects).

US STUDIES (Va TENOLOL-% PLACEBO):
CARDIOVASCULAR bradycarda (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%).
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR. dizziness (4%-1%), vertigo (2%-0.5%), light-headedness (1%-0%), itredness (0.6%-0.5%), faitigue (3%-1%), lethargy (1%-0.6%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0.0%-0.0%), dyspnea (0.6%-1%).

TOTALS US AND FOREIGN STUDIES:
CARDIOVASCULAR bradycarda (3%-0%), cold extremities (12%-5%), postural hypotension

TOTALS US AND FOREIGN STUDIES:
CARDIOVASCULAR bradycarda (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)
CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR, dizziness (13%-6%), vertigo (2%-0.2%), light headedness (3%-0.7%), trendenses (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)
GASTROINTESTINAL diarrhea (3%-2%), nausea (3%-1%)
RESPIRATORY (see WARNINGS), whee ziness (3%-3%), dyspnea (6%-4%)
MISCELLANEOUS. There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

therapy
POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress. Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neurosystopometrics.

disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

Miscellaneous: The oculomizocutaneous syndrome associated with the beta blocker practiol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practicol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia. In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted Bradycardia: Atropine or another anticholinergic drug.

Heart Block (Second or Third Degree): Isoproterenol or transvenous cardiac pacemaker.

Congestive Heart Failure: Conventional therapy. Hypotension (Depending on Associated Factors): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

Bronchospasm: Arminophylline, isoproterenol, or atropine.

Hypoglycemia: Intravenous glucose.

DOSAGE AND ADMINISTRATION: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to duretic therapy. The full effect of this dose will usually be seen within one to two weeks if an optimal response is not achieved,

TENDRMIN may be used alone or concomitantly with other antihypertensive agents including thiazide type diuretics, hydralazine, prazosin, and alpha-methyldopa. Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73 m² (normal range is 100-150 mL/min/1.73 m²); therefore, the following maximum dosages are recommended for patients with renal impairment

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very other da

Patients on hemodialysis should be given 50 mg after each dialysis, this should be done under hospital supervision as marked falls in blood pressure can occur. **HOW SUPPLED:** Tablets of 50 mg atenolol (round, flat, uncoated, white tablet identified with TENORMIN 50 debossed on one side and NDC number 105 debossed and scored on the other side) are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets. Tablets of 100 mg atenok (round, flat, uncoated, white tablet identified with TENORMIN 100 debossed on one side and NDC number 101 debossed on the other side) are supplied in bottles of 100 tablets and unit-dose

packages of 100 tablets.

Protect from heat, light, and moisture. Store unit-dose package at controlled room temperature.

Inactive largedients: magnesium stearate, microcrystalline cellulose, povidone, sodium starch

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Heart Transplantation: A Therapeutic Alternative for Patients with End-Stage Cardiac Disease: The Texas Heart Institute Experience

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Abstract: Heart transplantation is now an accepted therapeutic modality for patients with end-stage cardiac disease whose condition is not amenable to conventional medical and surgical intervention. Since July 1982, 74 heart transplants have been performed at the Texas Heart Institute using cyclosporine immunosuppression with a 73% survival rate. Pretransplant diagnoses included ischemic cardiomyopathy (40.5%), idiopathic cardiomyopathy (36.4%), viral myocarditis (8.1%), and endocardial fibroelastosis, with congenital heart disease and rheumatic heart disease accounting for the remaining 15%. Infections and allograft rejection constituted the major causes of morbidity and mortality in our series. Improvements in selection criteria of donors and recipients, organ preservation, and postoperative immunosuppression have contributed to enhanced survival.

In July 1982, the Texas Heart Institute reestablished its program in cardiac transplantation using cyclosporine (CsA) for immunosuppression. Although the molecular mode of action of CsA is uncertain, it is known that the drug depresses helper T-cell function and its use in clinical organ transplantation has been highly encouraging.

Heart transplantation is now an accepted therapeutic modality and sometimes is the only alternative for a selected group of patients with end-stage cardiac disease whose condition is not amenable to conventional medical and surgical intervention. Patients who are incapacitated due to their underlying cardiac disease and patients who are critically ill and supported by a mechanical circulatory assist device can have another chance for life through cardiac transplantation. This article describes the clinical heart transplantation program at the Texas Heart Institute.

Indications and Candidate Evaluation

Heart transplantation is indicated in patients with endstage cardiac disease whose anticipated survival is less than 25% at one year. The most common causes of endstage cardiac disease in patients referred to the Texas Heart Institute for transplantation include ischemic cardiomyopathy, idiopathic cardiomyopathy, congenital heart disease, rheumatic heart disease, and endocardial fibroelastosis.

Contraindications to transplantation include evidence of active or dormant non-treated infection, malignancy, high pulmonary vascular resistance (>6 Wood units), severe chronic obstructive pulmonary disease, severe hepatic or renal dysfunction, peptic ulcer, psychosis, and serious psychosocial abnormalities. After the patient is submitted for evaluation, a thorough history is taken and physical exam and pathological studies performed, including comprehensive biochemical, microbiological, and immunological tests to exclude the possibility of underlying conditions that might preclude transplantation. A medical review board composed of transplant surgeons, administrative and financial officers, a cardiologist, social worker, and dietitian meets to discuss each case in detail for acceptance into the program. Once accepted, patients are placed on a waiting list until a suitable donor becomes available.

Donor Selection and Organ Procurement

Strict criteria should be adhered to in donor selection. The donor must be young (preferably ≤ 35 years of age). When an orthotopic transplant is planned, the donor's weight preferably should be 20-30 pounds above or below that of the recipient. A smaller weight is acceptable when heterotopic transplantation is to be done. The donor should be free of infection, systemic disease or malignancy. Inability to wean the donor from large doses of inotropic drugs, an episode of cardiopulmonary resuscitation, or evidence of myocardial ischemia on the EKG constitute contraindications for acceptance of the donor for heart transplantation.1 When chest trauma has occurred, the heart is inspected at the time of donor harvest to rule out myocardial injury before the donor is accepted. Once the donor has been accepted, a recipient is identified who is a suitable match for ABO-blood type

From the Division of Surgery and the Transplantation Unit, Texas Heart Institute, Houston, Texas

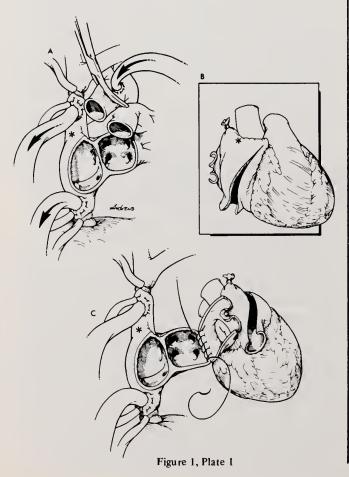
Address for reprints: Denton A. Cooley, M.D., Texas Heart Institute, P.O. Box 20345, Houston, Texas 77225

compatibility, size, and weight. Retrospective lymphocyte crossmatch is performed in every patient.

A team from the Texas Heart Institute is sent to procure the heart within a radius of 1,200 miles.² With adequate coordination of air travel and ground transportation, cardiac ischemic time can be kept under four hours, minimizing myocardial injury and allowing adequate return of function of the cardiac graft. By the time the procurement team arrives in Houston, a second group of surgeons has placed the recipient on cardio-pulmonary bypass.

Operation

Upon admission of the recipient, a physical examination and basic laboratory work-up are performed in preparation for the procedure. Cyclosporine (14 mg/kg) is given orally four hours prior to transplantation to obtain peak levels at the time of the operation. General anesthesia is induced and a median sternotomy performed. Cardiopulmonary bypass is instituted in the usual manner. After visual inspection of the graft, recipient cardiectomy is performed by incising the heart along the inferior atrioventricular groove. The aorta and pulmonary artery are transected above the semilunar valves. The apex of the heart is lifted, the interatrial septum and superior portion of the atria are transected, and the recipient's native heart is removed (Figure 1). Orthotopic heart transplantation is then performed as described by Cooley.3 When a heterotopic transplant is done, the



recipient heart is left in place and the new donor heart anastomosed in parallel, resting in the right pleural cavity (Figure 2).^{3, 4}

The patient is given 500 mg of intravenous methylprednisolone while on cardiopulmonary bypass. After the operation is completed, the patient is taken to the intensive care unit for immediate postoperative care and recovery.

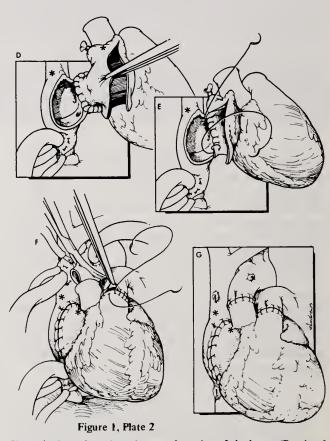


Figure 1. Steps in orthotopic transplantation of the heart. (Reprinted from *Techniques in Cardiac Surgery*, Second Editlon, 1984 (Denton A. Cooley), by permission of W.B. Saunders Co., Philadelphia).

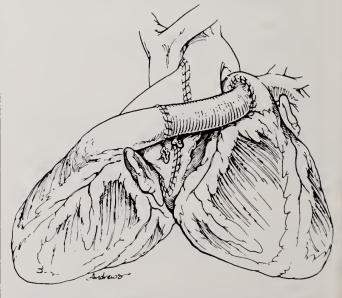


Figure 2. Drawing showing final step in heterotopic heart transplantation.

Postoperative Care

The immediate postoperative period resembles that following any elective open-heart surgical procedure. Special attention is given to bleeding, arrhythmias, and maintenance of adequate blood pressure and urine output. A continuous low-dose Isuprel drip is administered for 3-5 days. In addition, precautions are taken for infection control, including strict adherence to sterile techniques and hand washing. Patients are usually extubated within 24 hours.

Immunosuppression consists of CsA (14 mg/kg) given initially through a nasogastric tube and later orally. The dose is adjusted to maintain serum levels at 200-400 ng/cc. If indicated to maintain levels, intravenous CsA is given in addition to the oral dose. Prednisone is started orally after the last dose of methylprednisolone, beginning at 120 mg divided in four doses with daily tapering down to 20 mg/day by the 120th day. Daily chest roentgenograms, arterial blood gases, complete blood counts, and CsA trough levels are obtained for general monitoring as well as to detect early signs of CsA toxicity which will manifest as elevation in serum bilirubin and creatinine.⁵ Endomyocardial biopsies are performed weekly during the initial four weeks to detect signs of rejection. If histopathological signs of moderate to severe rejection are found, an additional dose of 500 mg of methylprednisolone is given intravenously every eight hours for six doses. Additional CsA is given if levels are inadequate. If histological improvement does not occur following this treatment, a course of equine antithymocyte globulin (ATG) is given (14 mg/kg IV daily). The white blood cell and platelet counts are monitored daily and the dose and duration of ATG therapy modified accordingly.

Other complications include those related to the immunosuppressed state and the use of CsA. Transplant patients are at high risk for serious bacterial, viral, and fungal infections. Infections by Candida albicans and Pneumocystis carinii are commonly reported in the immunosuppressed host.² To reduce the incidence of postoperative infection, special precautions are taken (e.g., all intravenous catheters, chest tubes, and the Foley catheter are removed as soon as possible). Numerous complications and side effects of CsA have been reported, including nephrotoxicity, hepatotoxicity, hypertension, tremors, hirsutism, and seizures. Pancreatitis has also been described and may be severe. 6 Close follow-up and monitoring of transplant patients during their hospital stay and after discharge are crucial in order to detect early signs of drug toxicity.

Results

In July 1982, a heart transplant program was initiated at the Texas Heart Institute using CsA and steroids for immunosuppression. From July 1982 to July 1985, a total of 74 heart transplants were performed (63 men and 11 women). Of these transplants, 71 were orthotopic and three were heterotopic. The mean age was 42 years.

The major pretransplant diagnoses were ischemic cardiomyopathy (40.5%), idiopathic cardiomyopathy (36.4%), and viral myocarditis (8.1%), with endocardial

fibroelastosis, congenital heart disease, and rheumatic heart disease accounting for the ramainder (15%). Fifty-four patients (73%) are alive, including our first patient done in 1982. Of the 20 patients who died, 10 (50%) died of infection, seven (35%) of rejection, two (10%) of arrhythmia, and one of other causes (nontransplant). Fifty-nine patients experienced one or more episodes of rejection, with seven fatal episodes. Thirty-nine patients experienced at least one episode of infection, and 10 of these episodes were fatal.

At the time of discharge, all patients were in NYHA functional Class I. Many of the patients have returned to their previous occupations and activities.

Discussion

Transplantation of the heart has developed from an experimental procedure to a widely accepted therapeutic alternative for the patient with end-stage cardiac disease not amenable to conventional medical or surgical treatment who has an expected survival less than 12 months if a transplant is not performed. With the advent of CsA as an immunosuppressive agent, survival rates have improved markedly and are 80% and 50% at one and five years, respectively.7, 8-9 Improvements in selection criteria of donor and recipient, organ preservation, and surgical techniques have also contributed to the increase in survival. Following transplantation, recipients lead active, high-quality lives. They are in good physical condition and can function socially again. With adequate follow-up, early detection of rejection, infection, and drug toxicity can be achieved.

Rejection still poses a problem for organ transplantation. With CsA immunosuppression, rejection can be present without clinical symptoms and can only be detected by routine endomyocardial biopsy. When symptoms are present, rejection is usually severe. At other times, rejection may be heralded by an acute onset of arrhythmias or by nonspecific symptoms and general malaise. Endomyocardial biopsy is indicated whenever rejection is suspected. In our patients, the most common cause of death is infection, an inherent risk of the immunosuppressed state. Close surveillance immediately postoperatively and during treatments of rejection episodes is mandatory. During this time, patients take high doses of steroids and are more prone to various types of infections.

Conclusion

Heart transplantation is an effective-treatment that can give the terminally-ill cardiac patient a second chance for life. Patients should be advised of this alternative before end-stage damage to other organs has occurred and before the patient is too ill to undergo a major operation. Thus, early referral and evaluation for transplantation is warranted in patients whose quality of life is markedly affected by their cardiac status. Few terminal illnesses can be treated so successfully. Young patients with idiopathic cardiomyopathies are particularly amenable to successful treatment and should not be denied the opportunity for survival afforded by cardiac transplantation.

Resumen: El transplante del corazón es una modalidad terapéutica aceptada para aquellos pacientes que sufren de enfermedad cardíaca terminal y cuya condición no es corregible mediante los tratamientos médicos o quirúrgicos convencionales. Desde julio de 1982, el "Texas Heart Institute" ha llevado a cabo 74 transplantes cardíacos usando la Ciclosporina como agente inmunosupresivo con una sobrevivencia de 73%.

Los diagnósticos antes del transplante incluyeron cardiomiopatía isquemica (40.5%), cardiomiopatía idiopática (36.4%), miocarditis viral (8.1%). La fibroelastosis endocárdica, las enfermedades congénitas y reumática cardíaca completaron el restante 15% de los casos. En nuestra serie, las infecciones y episodios de rechazo constituyeron las mayores causas de mortalidad y morbilidad. Las mejoras y avances en los criterios de selección de donantes y recipientes, en la preservación de órganos y en la inmunosupresión postoperatoria han contibuido a mejores resultados y mayor sobrevivencia.

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Intensive Surveillance of Pregnancy-Related Deaths, Puerto Rico, 1978-1979

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José G. Rigau-Pérez, M.D.³
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To provide a more accurate estimate of pregnancy-related mortality and a better understanding of associated risk factors, we conducted intensive surveillance of pregnancy-related deaths in Puerto Rico in 1978 and 1979. By expanding surveillance through review of death certificates and selected medical records, we identified 45 pregnancy-related deaths in addition to the 17 identified through vital statistics alone. Death certificates did not mention pregnancy or a pregnancy-related condition in 52% of pregnancy-related deaths. Our definition of pregnancy-related deaths included those occurring within 1 year of termination of pregnancy as opposed to the commonly accepted cutoff point of 42 days postpartum. Although the number of pregnancy-related deaths was only 6% higher than it would have been had we observed a 42day cutoff point, we learned valuable information about the risk factors associated with those pregnancy-related deaths occurring more than 42 days postpartum. Review of death certificates and selected medical records is an effective method for intensive surveillance of pregnancy-related mortality.

To be most effective in reducing pregnancy-related mortality, we need to evaluate associated risks and concentrate on reducing them. In evaluating risk factors, we need the most accurate estimates of pregnancy-related mortality that can be obtained, as well as information on the range and relative importance of risk factors associated with it. In estimating the extent of pregnancy-related mortality in Puerto Rico we looked first at vital statistics, which demonstrated a progressive decline in maternal mortality to a low of 5 maternal deaths per 100,000 live births in 1978. While vital statistics have shown a similar decrease in maternal mortality in the United States, it is widely recognized from studies using

improved surveillance that more pregnancy-related deaths occur than are documented by vital statistics.³⁻¹² Therefore, we felt that expanded surveillance in Puerto Rico might provide a more accurate estimate of the extent of pregnancy-related mortality and a better understanding of the associated risk factors. We initiated intensive surveillance of pregnancy-related deaths in Puerto Rico in 1978 and 1979 through review of death certificates and selected medical records. Surveillance was accomplished through the support of the Puerto Rico Department of Health and the cooperation of physicians, administrators, and staff in public and private hospitals throughout the island.

Methods

We defined a pregnancy-related death as a death which occurred during pregnancy or within (\leq) 1 year of its termination and which was related to pregnancy or its management. The pregnancy-related mortality ratio is the number of pregnancy-related deaths per 100,000 live births.

There were 1,709 deaths among women 10 to 49 years of age in Puerto Rico in 1978 and 1979. We reviewed 1,704 (99.7%) death certificates to determine if there were certificates which listed a complication of pregnancy, childbirth, or the puerperium as the underlying cause of death in addition to such deaths already reported in the State's vital statistics. We also sought to identify death certificates which mentioned a pregnancy-related condition, even though it was not considered the underlying cause of death. When we identified death certificates which mentioned pregnacy or a pregnancy-related condition, we examined medical records to establish whether the death met our definition of a pregnancyrelated death and to determine associated risk factors. In the one death for which we were unable to locate medical records, the death certificate attributed death to eclampsia, which we considered a pregnancy-related

To determine if there were more pregnancy-related deaths in which the physician had not listed pregnancy or a pregnancy-related condition on the death certificate, we selected 720 such death certificates for review of medical records. To conserve resources it was decided not to review those medical records in which it seemed highly unlikely from review of the death certificate that pregnancy might have played a role in the death. Thus deaths

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attributed to cancer, automobile accidents, drownings, and the like were not selected for review of medical records. In review of death certificates there appeared to be a continuum in the likelihood that pregnancy might have played a role in the death. On the other end of the scale were deaths attributed to such conditions as hypovolemic shock, sepsis, and thromboembolism in which there was considered a greater likelihood that pregnancy might have played a role. These were selected for review of medical records. We felt pregnancy might have played a role in these deaths, although the certificates did not mention pregnancy or a diagnosis readily identified with pregnancy. We visited 14 government hospitals and 26 private hospitals in 13 cities and towns throughout Puerto Rico, and the Institute of Forensic Medicine, in San Juan and reviewed 623 medical records. We wrote or called physicians and small health centers about an additional nine deaths. In all, 632 medical records were reviewed, 88% of those selected. We could not locate medical records for the remaining 88 death certificates. In no instance was access to medical records refused. After examining medical records, the reviewer classified deaths as pregnancy-related if they clearly fit our definition. In questionable cases, three obstetricians discussed the deaths and reached a consensus.

Results

We identified nine certificates on which the underlying cause of death had been coded as a complication of pregnancy, childbirth, or the puerperium. In addition we examined eight death certificates which listed eclampsia as the underlying cause of death, but these deaths had not been identified as maternal deaths in vital statistics because they were inappropriately coded under convulsions in a category for "Symptoms, Signs and Ill-Defined Conditions". Correction of this coding error enabled the Office of Statistics to identify a total of 17 deaths in 1978 and 1979 for which a complication of pregnancy, child-birth, or the puerperium was coded as the underlying cause of death (Table I). On review of medical records for these deaths, each met our definition of a pregnancy-death.

Fifteen death certificates mentioned pregnancy or a pregnancy-related condition, but another disease or condition was considered the underlying cause of death. On review of medical records for these deaths, 13 met the definition of a pregnancy-related death. On review of 632 medical records, we identified an additional 32 pregnancy-

Number and Percentage of Pregnancy-Related Deaths Identified
By Method of Surveillance, Puerto Rico, 1978-1979

Method of Surveillance	Pregnancy-Related Deaths			
	Number	Percentage		
Vital Statistics*	17	27		
Review of Death Certificates	13	21		
Review of Selected Medical Records	32	52		
Total	62	100		

^{*}After correction of coding error.

related deaths in which pregnancy or a pregnancy-related condition had not been mentioned on the death certificate (Table I).

Vital statistics identified 27% of the pregnancy-related deaths. Insufficient documentation on the death certificate was the main reason pregnancy-related deaths were underreported. In 52% of the pregnancy-related deaths, the death certificate did not mention pregnancy or a pregnancy-related condition. Correction of the coding error changed the ratio as reported in the State's vital statistics from 5 to 12 pregnancy-related deaths per 100,000 live births in 1978. However, ratios of 47 in 1978 and 37 in 1979 more accurately reflect the extent of pregnancy-related mortality in Puerto Rico for those years (Table II).

TABLE II

Pregnancy-Related Mortality Rations¹By Method of Surveillance,

Puerto Rico, 1978-1979

Method of Surveillance	Pregnancy-Related N	Mortality Ratios ¹
Vital Statistics ²	1978	1979
Review of Death Certificates and Selected Medical Records	1 47	37

¹Pregnancy-related deaths per 100,000 live births.

Our definition of pregnancy-related deaths included those occurring within 1 year of termination of pregnancy as opposed to the commonly accepted cutoff point of 42 days postpartum. Although the number of pregnancy-related deaths was only 6% higher than it would have been had we observed the 42-day cutoff point, we learned valuable information about the risk factors associated with those pregnancy-related deaths.

Of the 62 pregnancy-related deaths, 44 died following the termination of pregnancy. Termination includes delivery, resection of an ectopic pregnancy, and evacuation of an abortion or hydatidiform mole.

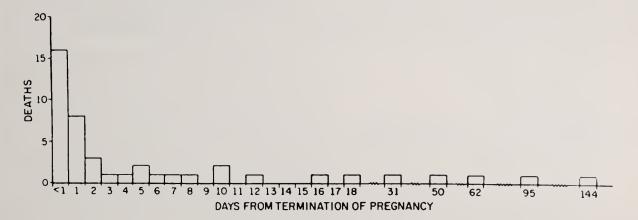
Four deaths (6%) occurred more than 42 days postpartum (Figure). One woman died 50 days postpartum with retroperitoneal abcesses after a cesarean section. Another woman died 62 days postpartum after further surgery for persistent postpartum bleeding. Developing subacute bacterial endocarditis within 1 week of her delivery, a woman with known rheumatic heart disease died 95 days postpartum from endocarditis. A 17-year old girl developed congestive heart failure at the time of her delivery and died 144 days postpartum from cardiomyopathy. We did not find any cases similar to these among the deaths which occurred within 42 days postpartum.

Idiopathic hypertensive disease of pregnancy was the most important medical risk factor for death we encountered, followed by hemorrhage and infection. Evaluation of risk factors associated with pregnancy-related deaths in Puerto Rico in 1978 and 1979 is the subject of a separate paper.¹³

²After correction of coding error.

FIGURE 1

DAYS FROM TERMINATION OF PREGNANCY UNTIL DEATH
FOR 44 PREGNANCY RELATED DEATHS, PUERTO RICO, 1978-1979



Discussion

We are interested in pregnancy-related mortality as an indicator of the effectiveness of women, their physicians, and the health care system in achieving safe and healthy pregnancies. We recognized that the more complete the surveillance, the more accurately we could chart our progress. We felt that our efforts to reduce pregnancy-related mortality would be more effective if we could evaluate risk factors and concentrate on reducing high risks. We knew that more complete surveillance would allow us to better identify the range and relative importance of risk factors associated with pregnancy-related deaths.

We recognized from studies elsewhere in the United States that pregnancy-related deaths identified in vital statistics are deaths for which the underlying cause of death reported on the death certificate is coded as a complication of pregnancy, childbirth, or the puerperium. Thus vital statistics do not include deaths in which pregnancy was a contributing factor but was not considered the underlying cause. Insufficient documentation on the death certificate has been widely recognized as a major cause of underreporting of pregnancy-related deaths in vital statistics. To the underlying of pregnancy-related deaths in vital statistics.

For many years maternal mortality committees and departments of health in some States have utilized reports from physicians, hospitals, medical record librarians, medical examiners, and news media to expand surveillance beyond the use of vital statistics. Through improved surveillance of this type, the New Jersey State Department of Health identified 26 maternal deaths in addition to the 30 reported in vital statistics in 1974 and 1975, an increase of 87% in case ascertainment. ¹² Linkage of death certificates of reproductive-age women with birth certificates has been widely used to aid in identifying pregnancy-related deaths. ⁷ In Georgia, computer linkage of death certificates with birth certificates led to a 50% increase in identification of maternal deaths over that reported in vital statistics for 1975 and 1976. ¹⁰

To provide expanded surveillance of pregnancyrelated deaths in Puerto Rico, we reviewed death certi-

ficates and selected medical records. This method of intensive surveillance proved effective, and we identified 45 pregnancy-related deaths in Puerto Rico in 1978 and 1979 in addition to the 17 identified through vital statistics. Of the 45 pregnancy-related deaths identified through expanded surveillance, 18 (40%) were associated with stillbirth, undelivered pregnancy, ectopic pregnancy, abortion, or hydatidiform mole and would not have been reported in a system linked to live births (Table III). We increased the efficiency of our review of medical records by excluding deaths attributed to cancer, automobile accidents, drowings, etc., since we considered it unlikely that pregnancy had contributed to the risk of death in these cases. For those contemplating such a review it is well to remember that one cannot expect to recover every pregnancy-related death. The goal is to identify as many pregnancy-related deaths as possible within the limits of available resources. If resources are scarce, most of the records in this middle zone may be excluded from further review. If more resources are available, an increasing number of these deaths may be selected for review of medical records. Subjective judgments are involved in deciding which deaths should be excluded from review, and a physician with specialty experience in the management of pregnancy and its complications is best equipped to make such decisions.

We considered excluding other categories of death based on the diagnostic code for the underlying cause of death. The 720 death certificates which we selected for review of medical records were distributed among 12 diagnostic code categories, and pregnancy-related deaths were identified in nine of these categories (Table IV). The three diagnostic code categories in which no pregnancy-related deaths occurred occounted for only 7% of the medical records selected. We concluded that we could not substantially increase the efficiency of medical record review through further exclusion of deaths by diagnostic code category.

One can increase efficiency by excluding from review the upper or lower limits of the age group under surveillance. Of the deaths from all causes among women 10 to 49 years of age, 5% occurred in the age group 10 to 14 and

TABLE III

Pregnancy-Related Deaths by Outcome of Pregnancy and Method of Surveillance, Puerto Rico, 1978-1979

	Method of Surveillance			
Outcome of Pregnancy	Vital Statistics	Review of Death Certificates and Selected Medical Record		
Delivered, Live Birth	9	24		
Delivered, Fetal Outcome				
Unknown to Investigator	0	2		
Delivered, Stillbirth	2	5*		
Undelivered	5	8*		
Ectopic Pregnancy	1	2*		
Abortion	0	2*		
Hydatidiform Mole	0	1*		
Outcome of Pregnancy				
Unknown to Investigator	0	1		
Total	17	45		

^{*}Pregnancy-related deaths which would not have been identified by surveillance linked to live birth certificates.

TABLE IV

Distribution of Death Certificates, Medical Records, and Pregnancy-Related Deaths by Diagnostic Code of the Underlying Cause of Death, Puerto Rico, 1978-1979

		Death Certificates of Women 10 to 49	Death Certificates Selected for Review	Medical Records	Pregnancy-Related Deaths Identified through Review of Medical Records	
ICD Code ¹	Category ²	Years of Age	of Medical Records	Reviewed	Number	Percentage ³
001-139	Infection	50	25	20	1	5
140-239	Neoplasm	378	0	_**	-	-
240-279	Endocrine	54	36	31	1	3
280-289	Blood	17	13	11	3	27
290-319	Mental	10	0	-	-	-
320-389	Nervous	78	43	38	0	0
390-459	Circulatory	337	284	252	10	4
460-519	Respiratory	154	128	117	7	6
520-579	Digestive	124	102	81	4	5
580-629	Genitourinary	43	30	28	1	4
630-679	Pregnancy	17*	-	-	-	-
680-709	Skin	5	0	-	-	-
710-739	Musculoskeletal	18	1	1	0	0
740-759	Congenital	19	8	8	0	0
760-779	Perinatal	0		-	-	-
780-799	lll-defined	41	37	33	3	9
800-999	lnjury	359	13	12	2	17
Total		1,704	720	632	32	5

¹Code of the underlying cause of death according to the International Classification of Diaseases, 9th Revision, Clinical Modification, (ICD-9-CM).

24% in the age group 45 to 49. In our study one death occurred in each of these age groups. A 14-year old girl died at 22 to 24 weeks' gestation with peritonitis following appendiceal rupture. A woman 47 years of age died with idiopathic hypertensive disease of pregnancy. We included these age groups because the risk of death is increased in the relatively small numbers of pregnancies which occur at the extremes of reproductive life. 9, 18 However, limited resources and the need for efficiency might prompt one to exclude from review deaths among

45-to-49-year old women. In Puerto Rico the age-specific fertility rate for women 45-49 years of age was 1.4 in 1978. In countries where fertility in the 45-49 year age groupo is higher, there may be greater need to review deaths in this age group.

An important issue in the surveillance of pregnancy-related deaths is the length of time following termination of pregnancy which one includes in the definition. Some (including the Puerto Rico vital statistics reports) limit this period to 42 days after termination of pregnancy,

²Abbreviated description of 1CD code category.

³Pregnancy-related deaths divided by medical records reviewed times 100.

^{*}After correction of coding error.

^{**&}quot;-" means not applicable.

others use 90 days.^{14, 19-21} Our definition included deaths which occurred within 1 year after termination of pregnancy, a position also taken by the Department of Health and Social Security in England.²² Thus we were able to evaluate risk factors different from those related to deaths occurring within 42 days of the termination of pregnancy.

Deaths which occur more than 42 days postpartum are associated with different kinds of disease and conditions than those deaths which occur soon after pregnancy. Of 4 pregnancy-related deaths associated with heart disease, 2 women with congestive heart failure secondary to mitral stenosis died during pregnancy. The deaths associated with subacute bacterial endocarditis and with cardiomyopathy occurred relatively late, well beyond 42 days postpartum. If we limit our evaluation to deaths within 42 days, our understanding of heart disease as a risk factor for pregnancy-related deaths will be limited. The death following further surgery for persistent postpartum bleeding and the death associated with retroperitoneal abscesses following cesarean section likewise occurred relatively late in the post-partum period after complicated courses of illness different from those associated with deaths which occurred within 42 days.

We feel that pregnancy-related death is a more useful and accurate term than maternal death. Although definitions of maternal death specify that deaths are included irrespective of the duration or site of pregnancy, we have encountered physicians who questioned whether deaths associated with abortion, ectopic pregnancy, or hydatidiform mole need to be reported as maternal deaths. 14,19-20

This study demonstrated that review of death certificates and selected medical records is an effective method of expanded surveillance, which provided a more accurate estimate of pregnancy-related mortality in Puerto Rico for 1978-1979. Surveillance of pregnancy-related mortality throughout the United States would be useful in establishing health priorities on a State, regional and national level and in developing measures to reduce pregnancy-related mortality. When successfully implemented, surveillance should expand to include perinatal mortality as well.²³⁻²⁴

Para conseguir un estimado más exacto de la Resumen: mortalidad relacionada al embarazo, y para comprender mejor los factores de riesgo asociados a esa mortalidad, llevamos a cabo una investigación intensiva de las muertes relacionadas al embarazo en Puerto Rico en 1978 y 1979. En contraste con las 17 muertes identificadas en las estadísticas vitales, una vigilancia expandida, mediante la inspección de certificados de defunción y récords médicos selectos, encontró 45 muertes adicionales relacionadas al embarazo. Los certificados de defunción no mencionaban embarazo o condiciones relacionadas al embarazo en 52% de las muertes relacionadas al embarazo. Nuestra definición de muerte relacionada al embarazo incluye las muertes que ocurrieron hasta un año del término del embarazo, en contraste con el período comúnmente aceptado de 42 días después del parto. Aunque el número de muertes relacionadas al embarazo fue sólo 6% mayor que si hubiéramos

observado sólo el período de 42 días, aprendimos información valiosa sobre los factores de riesgo asociados a esas muertes relacionadas al embarazo que ocurrieron más de 42 días después del parto. La inspección de certificados de defunción y récords médicos selectos es un método efectivo para la vigilancia intensiva de mortalidad relacionada al embarazo.

Acknowledgments

The authors wish to thank Carl W. Tyler, Jr., M.D., Roger W. Rochat, M.D., David A. Grimes, M.D., and Howard W. Ory, M.D., for their critical review of the manuscript and helpful suggestions.

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- A NUESTROS PATROCINADORES -

En este año a punto de terminar, la Junta Editora desea expresar su agradecimiento a nuestros patrocinadores del Boletín de la Asociación Médica de Puerto Rico, quienes con su apoyo, permiten nuestra labor y el logro de nuestros objetivos. Son éstos proveer un medio para la publicación de artículos científicos de nuestros médicos, informar a nuestros lectores de problemas médicos de importancia, proporcionar vías de comunicación para expresar puntos de vista; tanto oficiales como de índole personal, estimular liderato médico para la solución de nuestros problemas; en fin, lograr una revista de actualidad que refleje la calidad de la medicina Puertorriqueña.

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ARTICULOS ESPECIALES

Joint Commission on Accreditation of Hospitals, What for?

Ernesto Sánchez Molano, M.D., F.A.C.U.R.P.*

an hospitals survive without certification of the Joint Commission on Accreditation of Hospitals? (JCAH) Certainly yes. Do hospitals survive without compliance of the standards issued for accreditation purposes by Joint Commission on Accreditation of Hospitals? Definitely not. Let us not be misguided. Standards issued by JCAH are the ultimate product of consensus among most prestigious professionals in the health care field. The Board of Commissioners of JCAH has 21 members,† composed of physicians leaders in different specialties of medicine, active members of the American College of Physicians, American College of Surgeons, American Medical Association, American Dental Association and the American Hospital Association, heads in Medical Schools and hospitals' clinical departments, and hospitals' executives as well as a Nurse.

There is no choice. Good quality, cost-effective practice in medicine is only the one that is carefully delineated by means of standards. The drafts of standards for Accreditation are referred to four hundred specialized health organizations and individual experts before they are finally adopted and included in the Accreditation Manuals.

A special standing committee of the JCAH Board of Commissioners, the Standards-Survey Procedures (SSP) Committee, is responsible for the development, preparation and screening of any new or revised standard. A representative of the JCAH's Policy Advisory Committee and four representatives from the Professional and Technical Advisory Committees for the hospital, psychiatric, long-term care, and ambulatory health-care programs serve in this committee. Of the fourteen members of the SSP Committee eight are physicians, one is D.M.D., M.D., one is a nurse and four are hospitals chief executives. In many instances ideas for the revision or development of standards are brought up by

concerned physicians, or local professional organizations outside the JCAH. The corporate number organizations also perform important role, such as reviewing the drafts by the AMA staff and all proposed changes are sent to the field two or three times.

"Once the JCAH has gathered all of the comments, developed a final draft and field tested the change for cost-effectiveness, the draft is sent to the SSP Committee, if found satisfactory, it is brought before the full Board of Commissioners", says Dr. John E. Affeldt, President of the JCAH. Through standards we have set goals to be achieved for the process of accreditation beginning in the survey.

What is the purpose of JCAH survey? Many health care professionals and executives today are quite conscious of the real value of accreditation by the JCAH. Once in a while you find others who believe that the whole work developed through standards, accomplishments and compliance is nothing but bureaucratic activity. Yet the process of survey constantly look at the best performance of practice in the best facility. Standards set the optimal norms and conditions for the management of the whole health care system. The standards of Accreditation Manual describe the requirements that must be fulfilled if an institution and its working people have the purpose to do their jobs in correct manner.

Are we really conscious of what correct performance means in Medicine? Some professionals are not in fact. The evergrowing instances of medicolegal cases are a clear demonstration that awareness of what quality performance means in Medicine is lacking to critical degree in some practicing physicians and other personnel. Which are the basic fundamentals for the accreditation of a health care institution? We can say that accreditation remains awardable when the institution demonstrates:

- a) safe, sufficiently equipped facilities (plant, technology and safety management).
- b) well organized Governing Body and Professional Staffs with coordinated performance under suitable by-laws.
- c) an effective Quality Assurance Program which shows full involvement of the whole institution in the

Director, Quality Assurance Program, University Hospital, Puerto Rico Medical Center, Río Piedras, Puerto Rico 00936

^{*}Certified American Board of Quality Assurance and Utilization Review Physicians

[†]Since 1981 one member was added representing the public interest, thus totalling 22,

process of detection, identification and correction of deficiencies, problems, and or improvement of the quality of patient care, along with a prevention system for protection of the people within its premises against risks.

Increasing demand for optimal care and money savings in the practice should make health care professionals understand that it is very important to assure that the delivery of care is safe, accurate, proper and of high quality. This is not mere rhetoric. Take an example in your hospital and design an evaluation process for appraisal of antibiotic usage, infection control, blood usage or appropriateness and quality of surgical cases and see if you do not find problems which must be resolved.

The quality in health care is as essential as the care itself, furthermore, low quality medical care may prove to be extremely harmful when leaving irreversible damage and even fatalities which could otherwise be prevented.

When dealing day to day with hard clinical problems it can be easy to overlook the delicate margin which separates the quality care from risky bold clinical decisions and perilous overdoing.

The more ever-confident the practitioner, the more prone to serious errors and troubles he is. The more questioning on self decisions the more accurate the final results. The essence of the Quality Assurance is self-questioning of professionals for correction of wrong-doings.

Accreditation by JCAH is by itself a positive status and influencing factor in court room deliberations and also obvious requirement for some funding programs and licensing processes. In some instances non-accreditation or loss of accreditation may have a serious impact in hospital's training programs, Medicare contracts and payments, and also upon state's licences for operation. Accreditation by JCAH may represent for society and governmental offices a warranty of good standing and satisfactory condition for medical care performance.

Fulfillment and compliance of standards ensure the hospital and its professionals almost complete protection against aggressive actions which result from medical malpractice. Essentially, standards call for good and safe practice, the logic underlying these truths has strong power.

During the survey some institutions diligently, perhaps anxiously try to conceal problems and deficiencies which may cause embarrasment. It has to be said honestly that such practice is erroneous and counterproductive. Problems and deficiencies unveiled and treated with corrective actions which show resolution process should not be concealed. The survey is intended to educate and supply advisory aid to personnel and the hospital.

Penalties are not the goals of JCAH survey but the promotion and stimulus for ever-improving the quality of care in medicine work. As we know, the survey may result in non-accreditation, accreditation with major contingencies, minor recommendations, or full accreditation for the three years period which may generally have some type interim re-evaluations on the recommendations given. Non accreditation may result from important

deficiencies which point to serious lack of safety and quality in patient care. For example; hazards in the electrical systems or equipments may represent such a high risk that absolute correction shall be done before any accreditation is granted. Accreditation can also be denied in those instances where no evidence of laws for the ordered, disciplined, organized staff and governing body exist.

No accreditation is possible in those cases where the Quality Assurance Program is not implanted, is not active or is ineffective. The Quality Assurance Program remains as the most accurate system for ensuring proper medical care. The review of clinical functions and the clinical performance of the professionals, who are responsible for the delivery of care, is certainly a critical process for ensuring that such care will bring optimal benefit instead of undesirable actions endangering or hurting people. Nobody, needless to say JCAH surveyors, will tolerate the lack of such ensuring system in a hospital or any health care facility.

Thus the accreditation of JCAH for a hospital means wellbeing for patients and professionals, safety, security, self-confidency of correct conduct and satisfaction of accomplished duty towards mankind and society.

Suggested Reading

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- Guides for Examination ABQAURP of the American College of Utilization Review Physicians 1984
- 3. JCAH Accreditation Manual for Hospitals 1985

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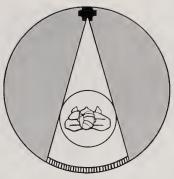


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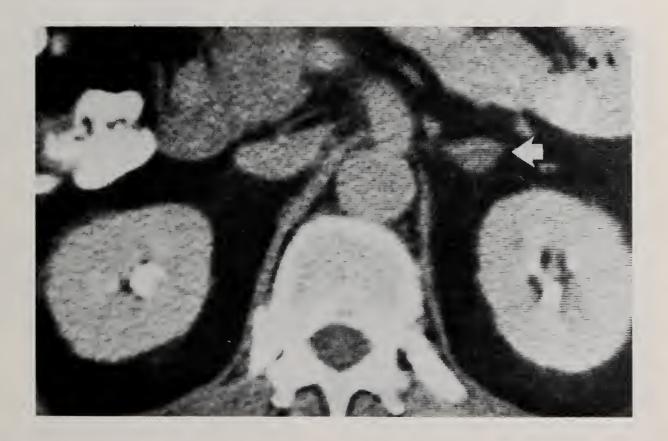
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Elsie Cintrón, M.D. * Tomás Jiménez, M.D. **

The figure below is a CT done to a 55 years old male patient with a 9 year history of uncontrollable hypertension, hypokalemia and hypernatremia.



WHAT IS YOUR DIAGNOSIS?

^{*}Chief, Radiology Service, San Juan VAH, Assistant Professor, University of Puerto Rico, School of Medicine

^{**}Staff Radiologist, San Juan VAH, Assistant Professor, University of Puerto Rico, School of Medicine

From the Department of Radiology, University of Puerto Rico, School of Medicine and San Juan V.A. Medical Center, San Juan, Puerto Rico



Figure 2. Focal left adrenal adenoma-within its posterior aspect.

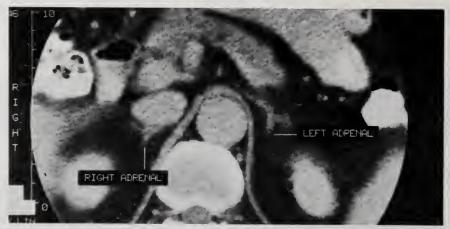


Figure 3. Cephalad section through adrenals. Normal appearing adrenal glands. Higher CT adrenal sections (Fig. 3) showed normal adrenal glands. This emphasizes the importance of narrow collimation and small increments when searching for adrenal tumors. Surgery confirmed a cortical cell adenoma.

Narrow CT scan increments and collimation should be used for evaluation of adrenal masses. In our institution, 5mm collimation and 4mm increments is the standard practice for adrenal CT studies.

DIAGNOSIS: Cortical Adrenal Adenoma (Aldosteronoma)

Selective adrenal vein sampling revealed aldosterone and low renin levels. A high resolution CT scan (Fig. 2) showed a focal left adrenal mass (1.4cm x 0.9cm) within its inferolateral limb posterior aspect.

Discussion

Primary aldosteronism is characterized by decreased plasma renin, hypokalemia and increased plasma aldosterone levels after sodium loading. The diagnosis is usually made with blood chemistry tests.

The most common cause of primary aldosteronism is an adrenal cortical adenoma. Distinction between an adenoma and hyperplasia as well as the localization of the tumor are essential for patient management. Adenomas are treated surgically whereas hyperplasia is managed medically.

CT plays an important role in accurate presurgical localization of functional adrenal neoplams. With the flank surgical approach, only one adrenal gland is explored; therefore, lateralization must be accurate. CT should be the first imaging study in patients with

biochemical evidence of primary aldosteronism. When CT is negative, adrenal venous sampling or I¹³¹ iodocholesterol radioisotope scanning may be helpful in excluding a small adenoma.

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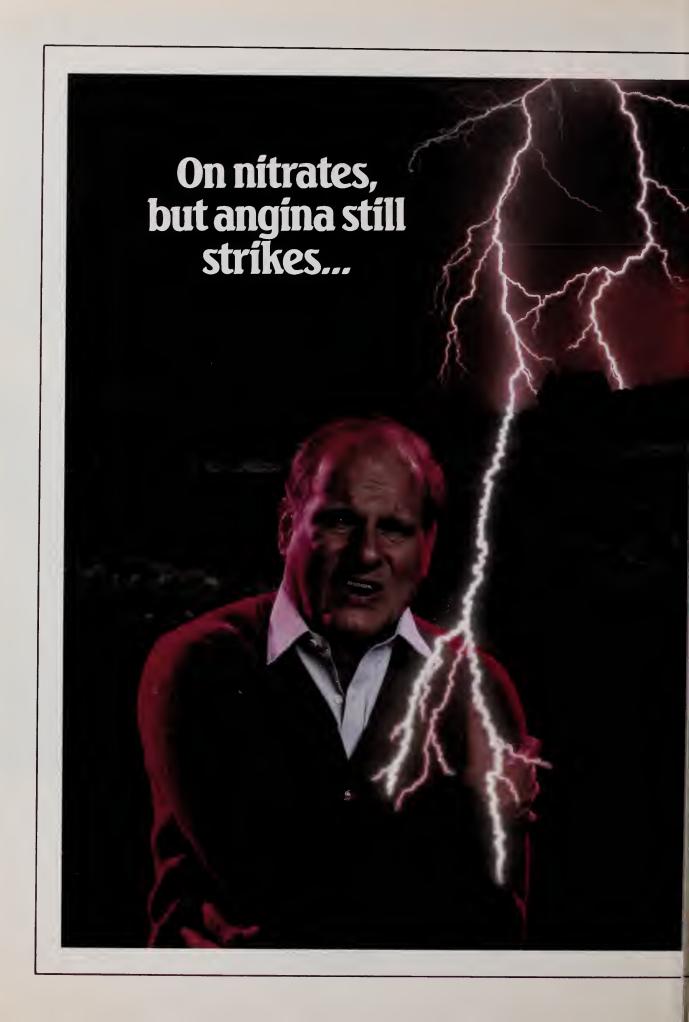
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Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations may disappear even with continued treatment; howreported. Such elevations may disappear even with continued treatment; now-ever, four cases of hepatocellular injury by verapamil have been proven by re-challenge. Periodic monitoring of liver function is prudent during verapamil therapy. Patients with atrial flutter or fibrillation and an accessory AV pathway (e.g. W-P-W or L-G-L syndromes) may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion, which has been used safely and effectively after ISOPTIN. Because of verapamil's effect on AV conduction and the SA node, 1° AV block and transient bradycardia may occur. High grade block, however, has been infrequently observed. Marked 1° or progressive 2° or 3° AV block requires a infrequently observed. Marked 1" or progressive 2" or 3" AV block requires a dosage reduction or, rarely, discontinuation and institution of appropriate therapy depending upon the clinical situation. Patients with hypertrophic cardiomyopathy (IHSS) received verapamil in doses up to 720 mg/day. It must be appreciated that this group of patients had a serious disease with a high mortality rate and that most were refractory or intolerant to propranolol. A variety of serious adverse effects were seen in this group of patients including sinus bradycardia, 2° AV block, sinus arrest, pulmonary edema and/or severe hypotension. Most adverse effects responded well to dose reduction and only rarely was verapamil discontinued. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patients should be carefully monitored to avoid over- or under-digitalization. ISOPTIN may have an additive effect on lowering blood pressure in patients receiving oral antihypertensive agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Clinical experience with the concomitant use of ISOPTIN and short- and long-acting nitrates suggest beneficial interaction without undesirable drug interactions. Adequate ani mal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C*: There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor and delivery only if clearly needed. It is not known whether verapamil is excreted in the prest milk: therefore, pursua should be discontinued during ISOPTIN use breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR < 50/min (1.1%), CHF or pulmonary ard degree (U.8%), bradycardia: HR < SU/min (1.1%), LFF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%), elevations of liver enzymes have been reported. (See Warnings.) 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PREVENTING LOW BIRTH WEIGHT INFANTS CAN SAVE HOSPITAL DOLLARS

Preventing low birthweight infants by screening and providing prenatal treatment for the mother at risk can significantly reduce the medical costs incurred in caring for these babies.

Richard Behrman, M.D., Professor of Pediatrics at Case Western Reserve University, Cleveland, reported at the American Academy of Pediatrics (AAP) Annual Meeting that when comparing the cost of standard prenatal medical screening of mothers to the costs of hospitalizing and caring for a low birthweight infant, millions of dollars in medical bills can be saved.

Dr. Behrman noted one of the leading causes of low birthweight babies centers on mothers not spacing babies more than six months apart through family planning.

He also added that "smoking significantly increases the risk of having a low birth weight infant." Other causes attributed to low birthweight infants are mothers who are hypertensive or have poor nutritional habits.

A recent Institute of Medicine (IOM) report covered strategies to prevent the birth of low birthweight infants who are at greatest risk of dying during infancy and suffering childhood morbidity. "It is especially important for mothers who have had reproductive problems involving conception or miscarriages to receive prenatal care and screening," said Dr. Behrman.

He added that simple medical screening and prenatal medical care to prevent the incidence of low birthweight babies is effective, but some mothers aren't receiving it because it is not always available to them.

Dr. Behrman stresed that the birth of underweight infants can be corrected and thus prevented. "It is a heart-breaking situation to have a child like this because young parents can be faced with bills of over \$100,000. That can affect the way the child and siblings are raised."

He added there is also an increased incidence of abuse and neglect with low birthweight infants that may stem from the social setting and can result in even more stressful situations.

Reducing the number of low birth weight infants by even a small amount (11.5 to 9 percent) can reduce medical bills by more than \$28 million, the IOM reported.

Rehospitalization of low birth weight infants can also be prevented, Dr. Behrman said, through counseling mothers. "Mothers who haven't had children before should receive specific infant feeding instructions. Mothers need to learn how to be alert for infection or other problems like diarrhea that can ultimately lead to rehospitalizing the baby," he concluded.

LAZINESS, UNDERACHIEVEMENT IN SCHOOL COULD SIGNAL SUBTLE DEVELOPMENT PROBLEM

A child in late elementary or junior high school who shows signs of fatigue, burnout, restlessness and low or inconsistent test scores may have an underlying, undiagnosed development problem.

So says Melvin Levine, M.D., Professor of Pediatrics at University of North Carolina, Chapel Hill, as he addressed a group of pediatricians at the Annual Meeting of the American Academy of Pediatrics (AAP).

He said that parents and teachers may often conclude that a restless, fatigued 9-15 year old is "just lazy" as school tasks become tougher and more complex, but signs like those may signify a developmental problem the child can't control—such as attention weakness, problems in memory and recall, or difficulty in fine motor coordination.

"Laziness and underachievement result more often from these hidden problems than from stresses like parental expectations or the pressure to perform," said Dr. Levine. In one preliminary study he is involved in, 17 percent of randomly selected 9-15 year olds had some sort of undiagnosed developmental problem.

"It's usually subtle," Dr. Levine explained. "A child may be able to think of words and ideas quickly, but putting them down on paper creates fear and chaos. There could be a justified reason for this, such as an awkward pencil grip."

Dr. Levine said that retraining the child's pencil grip or teaching him to type or use a word processor can help cure the problem. He stressed that the first step in determining how to solve the disorder is to pinpoint the individual child's strengths and weaknesses.

"Children really prefer to be successful," he said. "When they are lazy, the struggle has often become too difficult, the reasons for which may not be immediately apparent."

Memory problems are a common culprit. "Memory becomes increasingly important at this age, "Dr. Levine noted. "Spelling, writing, punctuation, capitalization, grammar; they all require memory skills. The details in subjects like math and history can boggle a child's mind."

Dr. Levine recommended teaching memorization techniques, active study methods and memory planning to help alleviate these problems. He also suggested that reducing the school load and allowing more time for tests would help a child with this type of disorder.

INCREASED ALCOHOL USE BY CHILDREN, TEENS MAY POINT TO MORE SERIOUS RISK-TAKING BEHAVIOR

Increased alcohol use by children and adolescents may be an early warning sign toward the development of more serious and damaging risk-taking behavior, such as drug use and even a suicide attempt, warned an expert who treats emotionally troubled youths.

Larry Silver, M.D., who addressed a joint session of the American Academies of Pediatrics and Child Psychiatry said that using alcohol is one of the more common ways that vulnerable children and adolescents move into serious risk-taking behavior. "Alcohol is socially acceptable in some peer groups," he said. "It also can make adolescents relaxed, outgoing, verbal and more socially active. Its use is rewarded with peer group approval."

Occasional drinking until drunk and restless behavior while intoxicated have been fairly conventional youth activities associated with growing up in America, said Dr. Silver, who is clinical director of the Devereux Foundation, Devon, Pa. "Alcohol use by adolescents is almost encouraged by our society. Free beer and cocktail parties abound at every college."

According to Dr. Silver, who was previously deputy director of the National Institute of Mental Health, early clues that might signify the development of more dangerous risk-taking behavior stemming from increased alcohol use include:

- a change in peer groups,
- a change in personality,
- a drop in school performance and grades,
- having colds; often and many,
- being sick at night, and,
- having an upset stomach Sundays or Mondays.

Dr. Silver said that often, parents and physicians miss these early warning signs that can lead to alcohol dependency —when adolescents drink for the feeling it gives them, not because of social acceptance.

Dr. Silver estimated that 10 to 20 percent of adolescents are problem drinkers. And, it is the child or adolescent who starts to interact with a peer group where alcohol and drug use are common—and not a youth with a vulnerable personality— who should be most closely watched by parents and physicians when he starts to drink.

The most commonly reported occasions in which teenagers are likely to drink, explained Dr. Silver, are at parties attended by peers with no adult supervision. One study found that students who drank with friends or alone were more likely to be problem users than those

who drank in front of parents or relatives. Dr. Silver noted that there is no particular type of "personality" at risk. "The use of alcohol comes first; the change in personality follows as a consequence."

The arrest rate for intoxication in those under 18 has tripled in the past decade. Dr. Silver said that problems can present themselves in recurrent truancy, stealing and other "acting-out" behavior. Dr. Silver's concern is that adolescents associate alcohol with adult status and do not perceive it as a dangerous drug.

SOUND FROM NOISY TOYS MAY HARM A CHILD'S HEARING

Two audiological researchers have found that sound from noisy toys may harm a child's hearing and as a result, recommend that parents limit the use of such toys by their children.

The researchers, from the University of Goteborg in Sweden, reported in the October issue of *Pediatrics*, the journal of the American Academy of Pediatrics (AAP), that although sensitivity to loud sounds in children is unknown, there is circumstantial data to indicate that children are more sensitive than adults, and tones or sounds at high frequencies can increase potential trauma to a child's ear.

Although manufacturers intend noise-emitting toys to be used in a sensible way, the researchers wrote, "it is easy to imagine the situation of a (toy) pistol or a gun pointed directly at or near the ear to a friend. If the gun barrel is open, such cases may result in immediate and persistent acoustic trauma."

In commenting on the study, Robert Prentice, M.D., AAP associate executive director for medical affairs, said the sound levels of these toys measured at a distance of 4 to 20 inches from the ear ranged in loudness from the noise produced by trucks passing on busy highways (78-108 dB) to the noise produced by jet engines at take-off (130-150 dB).

The study looked at several different categories of toys and found that toy weapons and firecrackers could cause the most potential hearing trauma. With toy weapons, the sound levels are so high that the study suggested using ear protectors in order to preserve normal hearing. Toys that emit snapping sounds such as machine gun-like noises, for example, also can achieve a level that could exceed hearing damaging levels.

Consequently, the researchers suggested that manufacturers label noisy toys with a warning statement mentioning that harm to a child's hearing is possible.

Teenage boys, the Swedish researchers noted, are often attracted to loud sounds and a significant number can suffer noise-induced hearing loss by the time they reach adolescence. Their study reported that boys age 12 to 15 are the most active in using firecrackers, which often are thrown carelessly and may explode close to the ear of friends. "It has been shown that the use of firecrackers results each year in a large number of cases of persisting hearing loss in boys," the researchers wrote.

Medical Specialties News Vol. 77 Núm. 12



American College of Cardiology

TWO-DIMENSIONAL ECHOCARDIOGRAPHY ASSISTS DECISION ON OPERATION FOR HYPOPLASTIC HEART

Two-dimensional echocardiography can help provide a complete anatomic diagnosis of hypoplastic left heart syndrome.

In a study by Dr. Stephen E. Bash and his colleagues, from Baylor College of Medicine and Texas Children's Hospital, 2-D echocardiography correctly diagnosed hypoplastic left heart syndrome in 13 of 15 neonates.

Furthermore, Dr. Bash said, echocardiography provided the necessary anatomic information to refer patients for palliative surgery without the need for cardiac catheterization.

Dr. Bash, a fellow in pediatric cardiology, presented the findings at the 34th Annual Scientific Session of the American College of Cardiology. His co-authors include Drs. James C. Huhta, Howard P. Gutgesell, and David A. Ott.

"It has previously been demonstrated that the gross anatomical diagnosis of hypoplastic left heart syndrome could be made with two-dimensional echocardiography," Dr. Bash explained. "Prior to the onset of palliative surgery, this was all that was necessary, because no further intervention was planned." However, with the introduction of palliative open-heart surgery—the so-called Norwood procedure—it became necessary to make a complete anatomic diagnosis to evaluate whether these patients were suitable candidates for surgery.

The aim of the present study was to determine whether 2-D/Doppler echocardiography could accurately diagnose hypoplastic left heart syndrome without the use of cardiac catheterization before surgery.

"In our study, we compared the anatomic findings of 15 neonates with hypoplastic left heart syndrome who underwent two-dimensional/Doppler echocardiography with results obtained by cardiac catheterization, surgery, or autopsy," Dr. Bash said. The mean age was 4 days.

2-D echocardiography delineated extracardiac structures, aortic arch configuration, pulmonary artery anatomy, pulmonary and systemic venous return, and atrial and ventricular morphology.

Echocardiography correctly identified in 5 of 8 patients a small left ventricular cavity (later demonstrated at autopsy) without producing any false positive or false negative results.

"Quantitative morphologic measurements by echocardiography of the aorta, pulmonary artery, and tricuspid valve annulus were not significantly different from autopsy findings," Dr. Bash observed.

In all, 2-D echocardiography was accurate in the

diagnosis of hypoplastic left heart syndrome in 86% of cases. There were two false-negative findings; however, both defects were identified later on the echocardiogram.

Complementary Doppler examination in 7 of the 15 patients identified retrograde aortic arch flow(6), prograde aortic arch flow (1), and right to left systolic shunting in 4 of 4 patients with patent ductus arteriosus.

In an interview with Cardiovascular News, Dr. Bash said the findings indicate that "echocardiography is accurate and that complete morphologic evaluation by echocardiography can identify all the necessary structures to send an child with hypoplastic left heart syndrome to surgery without the need for cardiac catheterization."

QRS CHANGES LOCATE AND MEASURE ISCHEMIA

Transient myocardial ischemia, such as occurs during variant angina, does indeed produce quantifiable changes in the QRS complex, investigators have shown. And these changes are related to the location and degree of ischemia.

According to Dr. Rafael F. Smith of the Veterans Administration Medical Center in Nashville, Tenn., application of these findings to conventional EKG interpretation may enable clinicians to determine more quickly and accurately the presence and location of coexisting ischemia in myocardial infarct patients, and to identify those patients who might benefit from early intervention.

Up until this time, cardiologists have had to rely almost solely on ST segment displacement in assessing ischemia. But this time-honored approach, Dr. Smith said, can be ambiguous.

"During ischemia, the ST segment can go up or down depending on the degree of ischemia, its location, whether it's transmural, etcetera," he explained to Cardiovascular News. "This prevents you from being able to rely on it as an accurate indicator of where the ischemia is."

In an article in *Circulation* (71:901, 1985), Dr. Smith and his colleagues from the Nashville VA Hospital and Vanderbilt University described a study in which computerized substraction techniques were used to analyze changes in the QRS complex during ischemia.

Data from five patients with vasospastic angina, three men and two women, were included in the analysis. All patients had spontaneous episodes of ischemic chest pain at rest and/or transient ST segment displacement of 0.2m V or greater. Three of the patients had electrocardiographic changes indicative of inferior ischemia and two had evidence of anterior ischemia.

Over a 24-hour period, electrocardiographic signals from Frank leads X, Y and Z on each patient were continuously recorded on FM magnetic tape. A total of 15 episodes of transient ischemia, lasting between 3 and 10 minutes, were detected. Using vectorcardiographic analysis, the researchers were able to "subtract" the

baseline QRS complex from that during ischemia and quantitatively assess the direction and degree of its change.

Dr. Smith's group found in all 5 patients that the QRS complex in the leads showing the greatest ST segment displacement consistently increased in amplitude, and that this change reached its peak during the last 40msec of the QRS. They also noted an increase in the duration of the QRS during ischemia. In several patients, a smaller change was noted in the initial 40 msec of th QRS and this change was electrically opposite to that observed in the terminal 40msec.

Perhaps most interesting was the investigators' finding through vector analysis that the "major changes" that occur in the terminal QRS vector correspond with the location of ischemia. Inferior wall ischemia produces a difference vector that points inferiorly, and anterior ischemia produces one that points anteriorly.

Their results were confirmed by similar studies in dogs, which showed also that peak QRS changes correlate highly with a decrease in conduction velocity and a rise in ventricular activation time.

"We are not the first to notice these QRS changes," Dr. Smith said. "People have observed changes they describe as 'giant R waves' during periods of ischemia. But these have all been qualitative observations." Dr. Smith said that his group undertook this study to determine if these changes could be quantified and, more importantly, to see if they were predictable. "We saw that there was a clear-cut pattern to what was occurring."

If this turns out to be a reliable measure, he said further, it could have a number of practical applications. For one, it could someday lead to a method of estimating infarct size using the EKG. Similar subtraction techniques have been used in the past to estimate the size of a myocardial infarct but, Dr. Smith said, EKG changes related to ischemia and not infarction may have been a real source of error in these estimations. If these newly learned principles are incorporated into the conventional EKG, it may result in a method of analysis that can more reliably assess whether the patient has an isolated MI or an MI and coexisting ischemia. In fact, Dr. Smith said, a subsequent study of 32 MI patients has shown that this method allows the detection of ischemia in another area of the heart, which may be complicating the MI. The presence of co-existing ischemia was confirmed by arteriography.

Secondly, because these principles help differentiate between infarction and ischemia, they may be used to identify rapidly MI patients at greatest risk. "Patients with an MI confined to one are have a certain risk of mortality depending on the size of the infarct. But patients who have coexisting areas of ischemia have a greater risk," Dr. Smith said. Earlier intervention for these patients may save lives.





UNNEEDED TESTS, PROCEDURES INFLATE MEDICAL COSTS

Medical costs can be best reduced by eliminating unnecessary tests and procedures, according to a report in JAMA.

The report suggests that a major and rapidly growing component of medical care costs stems from widespread application of tests and procedures that have no demonstrated benefit and may even be harmful.

"Identifying and curtailing such unnecessary medical care, rather than rationing beneficial technologies, should be the thrust of cost-containment efforts," asserts Marcia Angell, MD, deputy editor of the *New England Journal of Medicine*. She groups unnecessary care into three categories: "little-ticket" items such as x-ray films, which often have no indication and no benefit to the patient; "big-ticket" items, such as coronary bypass surgery, which may not be indicated for as many as 25 percent of those currently undergoing surgery; and aggressive treatment of terminally ill patients.

"Last year, in a large teaching hospital in New York, 10 percent of the hospital budget was spent on the final admissions of the 4 percent of patients who died in the hospital," Angel says. She notes that nearly half of these patients had diagnoses of cancer or other terminal disease. "Treating these patients much less aggressively and directing the treatment toward their comfort would in most cases be kinder, and it would secondarily result in very large savings," she observes.

Angell estimtes that these three categories of unnecessary medical care represent a cost of more than \$15 billion per year in the United States. In contrast, certain expensive, lifesaving medical procedures cost less as a whole. If heart transplants were performed on all patients who needed them, the cost per year would be about \$7.5 billion; and for liver transplants, less than \$1 billion. The idea of rationing is contrary to the physician's role as a patient advocate, Angell observes, and it is based on the false premise that more is better. "Cost containment should be seen as a matter of directing funds and services away from unnecessary care and toward beneficial care, even though the unit costs of the latter may be high," she says.

There is a large "gray area" between lifesaving procedures and unnecessary ones, Angell says, calling for much more effective technology assessment. "The data concerning the indications and medical risks and benefits of many of these procedures and practices are simply inadequate," Angell observes. "In the absence of data, the tendency is to act rather than refrain from acting."

Expenditures for unnecessary medical care are an inherent and growing part of the medical care system, Angell says. She proposes three methods to reverse this trend: revise fee schedules so that they neither encourage nor discourage the use of tests and procedures; undertake systematic studies to assess technologies and practices, and make every effort to discourage the practice of defensive medicine.

JAMA September 6, 1985

COMPUTER RECORD SYSTEM IMPROVES PATIENT CARE

New computer systems that summarize patient record information demonstrably improve the clinical decision process, according to a report from the University of California, San Francisco, that appears in JAMA.

Historically, physicians have relied on bulky patient medical records, often filled with subjective impressions, for information concerning patients' conditions. The Summary Time-Oriented Record (STOR) system used in the study provides a distillation of a patient's symptoms and physicians' laboratory tests to determine important clinical parameters.

In testing the new computerized system, Quinn E. Whiting-O'Keefe, MD, and colleagues sought answers to the question of which system, STOR or traditional medical records, brought more information to the physician making decisions. "The answer has substantial medical, ethical and legal implications," they say.

The system was tested in two ways. "In the first study, physicians were better able to predict their patients' future symptom changes and laboratory test results from outpatient visits to an arthritis clinic when STOR was added to the standard medical record than when the standard medical record was used alone," the researchers report.

"In a separate study, the removal of the standard medical record did not result in an important decrease in the physicians' ability to predict their patients' symptoms and laboratory test results, if they had the option of using the full paper record when they throught they needed it," they add, pointing out that in 134 of 514 patients visits the physicians exercised that option.

"We conclude that, for outpatient visits, the computerized record system operationally added information to that supplied by the full paper medical record. This improved flow of information could improve the clinical decision process," they say. Commenting on the system, the researchers point to two characteristics that account for its ability to improve physicians' predictive accuracy. First, it provides a legible summary of the most relevant and important clinical information in a well-defined and predictable format that eliminates the large amount of low-priority information on standard records. Second, the new system encourages the appreciation of information about time trends and the patterns of change in different kinds of variables.

JAMA September 6, 1985

RESEARCHERS IDENTIFY FACTORS IN CHILDHOOD ASTHMA DEATHS

A history of seizures, conflicts with parents and other factors influence the likelihood of childhood death from severe asthma, according to a report in JAMA.

Robert C. Strunk, MD, of the Jewish Center for Immunolgy and Respiratory Medicine, Denver, and colleagues evaluated records of 21 patients who had been hospitalized between 1973 and 1982 for treatment of severe asthma and who had died sometime after discharge. Average age at death was 13 years, with a range from 8 to 18 years. The researchers also studied the records of 21 controls matched for age, sex, severity of illness and time of hospitalization. The case-control study revealed that children who died from the disease were more likely to share certain medical and psychological characteristics.

The researchers found eight variables tha could be used to discriminate between the two groups of patients. These included history of seizures associated with an asthma attack, conflicts between the patient's parents and hospital staff regarding treatment, inappropriate self-care of asthma while in the hospital, prednisone dosage decreased by more than 50 percent during hospitalization, inhaled beclomethasone dipropionate required for treatment, increased asthmatic symptoms during the week before discharge, depressive symptoms and disregard of asthmatic symptoms.

The researchers believe theirs is the first study of childhood asthma deaths that included controls. The most striking finding was that certain psychological symptoms were present in addition to medical symptoms in ll children who died. "Most of the clinical characteristics previously thought to place patients at greater risk for a fatal asthmatic attack were found as often in the control cases as in the children who died," the researchers say. "These variables alone did not identify the patients who died unless there were also psychologic difficulties present".

Of th 57 physiologic and pshychologic variables studied, when compared with controls, 14 were present in significantly different percentages in the group of children who died of asthma. The researchers note that ten of these differentiating characteristics reflected the psychologic adaptation of the child or the child's family.

They add that one of the clinical variables, increased asthma during the last week of hospitalization, may have been psychologically based.

Pshychologic problems that were observed more often among children who died included parent-child conflict or other family dysfunction, manipulative use of asthma symptoms, despondency, deficient self-care and disregard of symptoms.

JAMA September 6, 1985

INTERFERON REDUCES MULTIPLE SCLEROSIS SYMPTOMS

Multiple sclerosis patients treated with human fibroblast interferon showed a marked reduction in disease symptoms, according to a report in the September Archives of Neurology. Lawrence Jacobs, MD, of the Dent Neurologic Institute in Buffalo, N.Y., and colleagues report follow-up findings on MS patients treated with interferon, showing that study patients' disease flare-ups have dropped from 1.8 per year to 0.16 after more than four years of treatment. Control patients transferred into the interferon group have shown a decrease of flare-ups to 0.30 per year after two years of treatment. "The toxic side effects of interferon beta administration intrathecally were acceptable in view of the benefit achieved," the researchers report.

SULINDAC MAY PREVENT VISION LOSS IN DIABETICS

Sulindac, a nonsteroidal antiinflammatory drug, appears to prevent blood-vessel alterations associated with vision loss in diabetic patients, researchers report in the September Archives of Ophthalmology. José G. Cunha-Vaz, MD, PhD, of the University of Illinois School of Medicine in Chicago, and colleagues compared sulindac treatment with placebo in a group of 24 insulindependent diabetic patients and found that treated patients "had a significant beneficial effect on the breakdown of the blood-retinal barrier." The say that long-term studies are now in order "to determine if the progression and development of the full-picture of diabetic retinopathy and final vision loss can be prevented."

REVIEW NON-HODGKIN'S LYMPHOMA IN PREGNANCY

Although relatively rare, cancer in pregnant women can have devastating effects, according to a report of three cases and a literature review appearing in the September Archives of Pathology and Laboratory Medicine. Harry L. Ioachim, MD, of Lenox Hill Hospital in New

York City points out that pregnancy and neoplasia share a capacity of growing cells that express foreign antigens. He adds that lymphomas during pregnancy are highly malignant and involve organs most stimulated, including breast, ovary and uterus. In the reported three cases, the mothers carried to term and delivered unaffected, healthy babies. But typically the mothers suffer rapid deterioration after delivery. Studies show that cancer affects one in 1,008 pregnancies.

CARDIOVASCULAR SURGERY SAFE FOR HYPOTHYROID PATIENTS

Major cardiovascular surgery can be performed safely in most patients with mild to moderate hypothyroidism, according to a study in the September Archives of Internal Medicine. Daniel J. Drucker, MD, of Massachusetts General Hospital in Boston, and Gerard N. Burrow, MD, of the University of Toronto, prospectively studied 500 patients requiring cardiac surgery and found ten with undiagnosed hypothyroidism. "All ten tolerated surgery well without preoperative thyroid hormone replacement," they say. They conclude that untreated hypothyroidism in patients with ischemic heart disease should not be an absolute contraindication to coronary artery bypass surgery.

PIGMENT CHANGES OBSERVED IN TREATED KIDNEY PATIENT

Severe pigment changes of hair and freckles occurred in a young kidney patient receiving chloroquine sulfate therapy, according to a report in the September Archives of Dermatology. Andre Dupre, MD, and colleagues from the Purpan Hospital in Toulouse, France, say a 15-year-old patient was referred to their department for evaluation of hypopigmentation. They point out that chloroquine is deposited in much greater concentrations in tissue than in blood and is normally excreted through kidney tubules. "Thus, the impaired tubular excretion must have greatly facilitated the hypopigmentation of hair and freckles in our patient through persistently high serum levels of chloroquine."

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El Boletín acepta para su publicación articulos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que

pudiera ser de interés general para la profesión médica. Se urge a los autores se esfuercen en perseguir claridad, brevedad, e ir a lo pertinente en sus manuscritos no importa el tema o formato del manuscrito,

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y la del impresor, se requiere de los autores que sigan las siguientes instrucciones:

Manuscrito

El manuscrito completo, incluyendo las leyendas y referencias deberán estar escritos en maquinilla a doble espacio; por un solo lado de cada página, en TRIPLICADO y con amplio margen. En página separada deberá incluirse lo siguiente: titulo, nombre del autor(es) y su grado (ej: MD, FACP), ciudad donde se hizo el trabajo, el hospital o institución académica, patrocinadores del estudio, si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse con un encabezamiento en letras

mayúsculas.

Ártículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: Introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias

Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: Introducción, Materiales y Métodos si es aplicable, Observaciones del Caso, Discusión, Resumen (en español e inglés), Reconocimientos y Referencias.

Nomenclatura

Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea. Se usará con preferencia el sistema métrico de pesos y medidas.

Tablas

Las tablas deben aparecer en hojas separadas. Estas deben incluir el título, y el número de la tabla debe estar en romano. Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales en la tabla. Se usará en las tablas el mismo idioma en el cual está escrito el articulo. Deben limitarse las tablas a solo aquellas que contribuyan al mejor entendimiento del manuscrito.

Ilustraciones

Las fotografías y microfotografías se someterán como copias en papel de lustre, sin montar o en transparencias. En el reverso de la figura debe aparecer el número de la figura (arábigo) y el autor. Debe indicarse la parte superior de la ilustración.

Resumen

Un abstracto no mayor de 150 palabras debe acompañar los manuscritos. Debe incluir los puntos principales que ilustren la substancia del artículo y la exposición del problema, métodos, resultados y conclusiones.

Las referencias deben ser numeradas sucesivamente de acuerdo a su aparición en el texto. Los números deben aparecer en parentesis al nivel de la linea u oración. Al final de cada articulo las referencias deben aparecer en el orden numerico en que se citan en el texto. Deben utilizarse solamente las abreviaturas para títulos de revistas científicas según indicadas en el "Cumulative Index Medicus" que publica la Asociación Médica Americana. Las referencias deben seguir el patrón que se describe a continuación.

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Se publicarán a discreción de la Junta Editora. Deben estar escritas en maquinilla a doble espacio, no deben ser mayores de 500 palabras, ni incluir más de cinco referencias.

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INSTRUCTIONS TO AUTHORS*

The Bulletin will accept for publication contributions relating to the various areas of medicine, surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

All authors are urged to seek clarity, brevity, and pertinence in the manuscripts regardless of subject or format.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

Manuscripts

The entire manuscript, including legends and references should be typewritten double spaced in TRIPLICATE with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgement of financial sponsors, and if the paper has been presented at a meeting the place and date should be given.

date should be given.

The manuscripts should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by headings in capital letters.

Articles reporting the results of clinical studies or laboratory investigation should be organized under the following headings: Introduction, Material and Methods, Results if indicated, Discussion, Summary in English and Spanish, Acknowledgments if any, and References.

Nomenclature

Generic names of drugs should be used; trade names may also be given in parenthesis, if desired. Metric units of measurement should be used preferentially).

Tables

These should be typed on separate sheets with the title and table number (Roman) centered. Symbol for units should be confined to the column headings. Vertical lines should be omitted. The language used in the tables must be the same as that of the article. Include only those tables which will enhance the understanding of the article. They should supplement, not duplicate the text.

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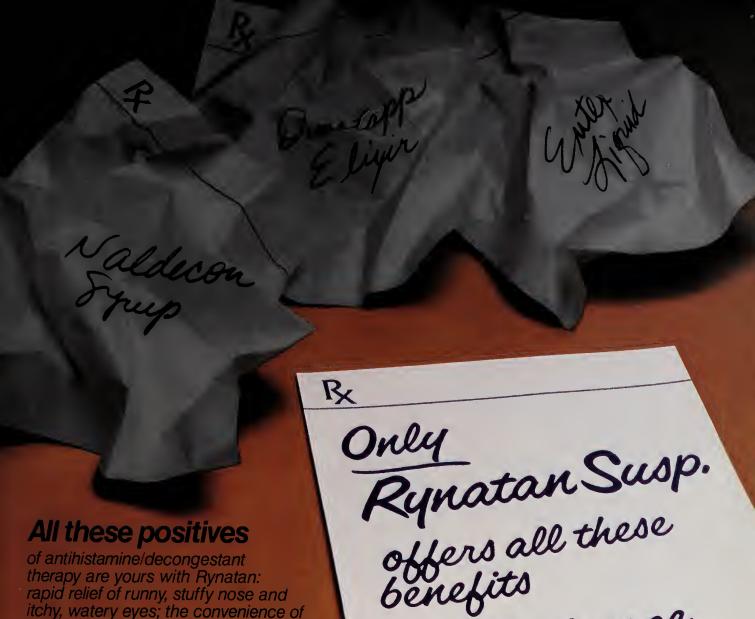
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Porque es bien rápido y fácil.



Porque te resuelve en emergencias.



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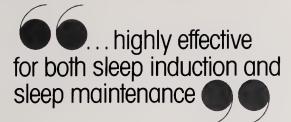




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EXCERPTS FROM A SYMPOSIUM "THE TREATMENT OF SLEEP DISORDERS"8



Sleep Laboratory Investigator Pennsylvania

conset of action is rapid...provides sleep with no rebound effect to agitate the patient the following day

Psychiatrist California

the best safety record of any of the benzodiazepines

Psychiatrist California

After 15 years, the experts still concur about the continuing value of Dalmane (flurazepam HCl/Roche). It provides sleep that satisfies patients... and the wide margin of safety that satisfies you.

The recommended dose in elderly or debilitated patients is 15 mg. Contraindicated in pregnancy.

DALMANE®
flurazepam HCI/Roche ®
sleep that satisfies

15-mg/30-mg
capsules

References: 1. Kales J, et al. Clin Pharmacol Ther 12 691-697, Jul-Aug 1971. 2. Kales A, et al. Clin Pharmacal Ther 18:356-363, Sep 1975. 3. Kales A, et al. Clin Pharmacal Ther 19:576-583, May 1976. 4. Kales A, et al. Clin Pharmacal Ther 32:781-788, Dec 1982. 5. Frost JD Jr, DeLucchi MR: J Am Geriatr Sac 27:541-546, Dec 1979. 6. Dement WC, et al. Behav Med, pp. 25-31, Oct 1978. 7. Kales A, Kales JD: J Clin Psychapharmacal 3:140-150, Apr 1983. 8. Tennant FS, et al. Symposium on the Treotment of Sleep Disorders, Teleconference, Oct 16, 1984. 9. Greenblott DJ, Allen MD, Shoder RI: Clin Pharmacal Ther 21:355-361, Mar 1977.



DALMANE*

flurazepam HCI/Roche (V

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nacturnal awakenings and/or early marning owokenings in patients with recurring insomnia or poor sleeping habits, in acute or chranic medical situations requiring restful sleep. Objective sleep loboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is offen fronsient and intermittent, prolonged administration is generally not necessory or recommended. Repeated therapy should only be undertaken with appropriate potient evaluation.

Controindications: Known hypersensitivity to flurazepam HCI, pregnancy Benzadiozepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital molformations associated with benzadiazepine use during the first trimester. Worn potents of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepom. Instruct potents to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting theropy.

Wornings: Coution potients about possible combined effects with olcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This patential may exist for several days following discontinuation. Caution against hozardous occupotians requiring camplete mental olertness (e.g., operating machinery, driving). Potential impoirment of performance of such octivities may occur the day following ingestion. Nat recommended for use in persons under 15 years of age. Withdrawal symptams rarely reported, obrupt discontinuation should be avoided with gradual tapering of dosage for those potients on medication for a prolonged period of time. Use coution in administering to addiction-prone individuals or those who might increase dosage.

Precoutions: In elderly and debilitated potients, it is recommended that the dasage be limited to 15 mg to reduce risk of oversedotion, dizziness, confusion ond/or ataxia. Consider potential additive effects with other hypnotics or CNS depressonts. Employ usual precautions in severely depressed potients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drawsiness, lightheodedness, staggering, ataxia and falling have accurred, particularly in elderly ar debilitated patients. Severe sedation, lethorgy, disorientation and cama, probably indicative of drug intolerance or overdosage, have been reported. Also reported. headache, heartburn, upset stomach, nausea, vormiting, diarrhea, constipation, Gl pain, nervousness, talkotiveness, apprehensian, irritability, weakness, palpitations, chest poins, body and joint pains and GU camplaints. There have also been rore occurrences of leukopenia, granulacytopenia, sweating, flushes, difficulty in facusing, blurred vision, burring eyes, faintness, hypotensian, shortness of breath, pruntus, skin rash, dry mouth, bifter toste, excessive solivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, holliucinations, and elevated SGOT, SGPT, tatal and direct bilirubins, and alkoline phasphatose, and paradoxical reactions, e.g., excitement, stimulation and hyperactivity

Dosoge: Individualize for maximum beneficiol effect *Adulls* 30 mg usual dosage. 15 mg may suffice in some polients *Elderly ar debililated patients*. 15 mg recommended initially until response is determined

 $\begin{tabular}{ll} \textbf{Supplied:} Copsules containing 15 mg or 30 mg flurazepam HCI \\ \end{tabular}$

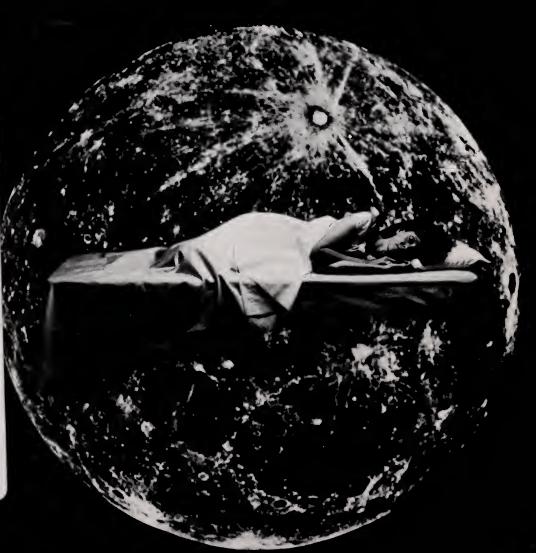


#1 FOR SLEEP

After more than 15 years of use, it's #1 for sleep that satisfies. Patients are satisfied because they fall asleep fast and stay asleep till morning. 1-8 And *you're* satisfied by the exceptionally wide margin of safety. 7-9 As always, caution patients about driving or drinking alcohol.

Please see references and summary of product information on reverse side

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